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(54) Title: NOVEL COMPOUNDS

(57) Abstract

The invention provides novel compounds, a process for their preparation, pharmaceutical compositions containing them, a process for preparing the pharmaceutical compositions, and their use in therapy.

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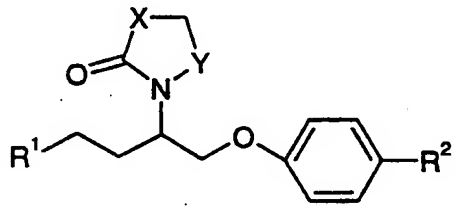
NOVEL COMPOUNDS

The present invention relates to novel compounds, a process for their preparation, pharmaceutical compositions containing them, a process for preparing the pharmaceutical compositions, and their use in therapy.

The $P2X_7$ receptor (previously known as P2Z receptor), which is a ligand-gated ion channel, is present on a variety of cell types, largely those known to be involved in the inflammatory/immune process, specifically, macrophages, mast cells and lymphocytes (T and B). Activation of the $P2X_7$ receptor by extracellular nucleotides, in particular adenosine triphosphate, leads to the release of interleukin-1β (IL-1β) and giant cell formation (macrophages/microglial cells), degranulation (mast cells) and L-selectin shedding (lymphocytes). $P2X_7$ receptors are also located on antigen-presenting cells (APC), keratinocytes, salivary acinar cells (parotid cells) and hepatocytes.

It would be desirable to make compounds effective as $P2X_7$ receptor antagonists for use in the treatment of inflammatory, immune or cardiovascular diseases, in the aetiologies of which the $P2X_7$ receptor may play a role.

In accordance with the present invention, there is therefore provided a compound of general formula



(I)

wherein X represents an oxygen or sulphur atom or a group NH, CH_2, CH_2CH_2 or OCH_2;
Y represents a group CH_2 or C=O;
R^1 represents a pyridyl (especially 3-pyridyl or 4-pyridyl) orpyrimidinyl group;
R^2 represents a phenyl, pyridyl or pyrimidinyl group, each of which may be optionally substituted by one or more substituents independently selected from a halogen atom or an amino, cyano, hydroxyl, nitro, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkylthio, (di)C_1-C_6-alkylamino, C_1-C_6-alkylcarbonyl, C_1-C_6-alkoxycarbonyl, C_1-C_6-alkylsulphinyl, C_1-C_6-alkylsulphonyl, $-NR^3SO_2R^4$ or $-SO_2NR^5R^6$ group, or a

group -Z-$(CH_2)_p$-Z-$(CH_2)_q$-H wherein each Z independently represents a nitrogen or oxygen atom, p is an integer from 2 to 5 and q is 0 or an integer from 1 to 5;
R^3 and R^4 each independently represent a hydrogen atom or a C_1-C_6-alkyl group; and
R^5 and R^6 each independently represent a hydrogen atom or a C_1-C_6-alkyl group, or together with the nitrogen atom to which they are attached form a pyrrolidinyl or piperidinyl group; or a pharmaceutically acceptable salt or solvate thereof.

In the context of the present specification, unless otherwise indicated, an alkyl substituent or alkyl moiety in a substituent group may be linear or branched and also the alkyl moieties in a dialkylamino substituent group may be the same or different. Furthermore, when X represents a group OCH_2, the oxygen atom is positioned adjacent the carbonyl group in the ring.

The group R^2 preferably represents a phenyl, pyridyl or pyrimidinyl group, each of which may be optionally substituted by one, two, three or four substituents independently selected from a halogen atom (e.g. fluorine, chlorine, bromine or iodine) or an amino, cyano, hydroxyl, nitro, C_1-C_6-alkyl (e.g. methyl, ethyl, propyl, butyl,pentyl or hexyl), halo-C_1-C_6-alkyl (e.g. trifluoromethyl), C_1-C_6-alkoxy (e.g. methoxy, ethoxy, propoxy, butoxy, pentoxy or hexoxy), C_1-C_6-alkylthio (e.g. methyl-, ethyl-, propyl-, butyl-,pentyl- or hexylthio),, (di)C_1-C_6-alkylamino (e.g. methylamino, dimethylamino, ethylamino or diethylamino), C_1-C_6-alkylcarbonyl (e.g. methyl-, ethyl-, propyl-, butyl-,pentyl- or hexylcarbonyl), C_1-C_6-alkoxycarbonyl (e.g. methoxy-, ethoxy-, propoxy-, butoxy-, pentoxy- or hexoxycarbonyl), C_1-C_6-alkylsulphinyl (e.g. methyl-, ethyl-, propyl-, butyl-, pentyl- or hexylsulphinyl), C_1-C_6-alkylsulphonyl (e.g. methyl-, ethyl-, propyl-, butyl-, pentyl- or hexylsulphonyl), -$NR^3SO_2R^4$ or -$SO_2NR^5R^6$ group, or a group -Z-$(CH_2)_p$-Z-$(CH_2)_q$-H wherein each Z independently represents a nitrogen or oxygen atom, p is an integer from 2 to 5 and q is 0 or an integer from 1 to 5.

More preferably R^2 represents a phenyl, pyridyl or pyrimidinyl group, each of which may be optionally substituted by one, two or three substituents independently selected from a halogen atom or an amino, cyano, hydroxyl, nitro, C_1-C_4-alkyl, halo-C_1-C_4-alkyl, C_1-C_4-alkoxy, C_1-C_4-alkylthio, (di)C_1-C_4-alkylamino, C_1-C_4-alkylcarbonyl,

C_1-C_4-alkoxycarbonyl, C_1-C_4-alkylsulphinyl, C_1-C_4-alkylsulphonyl, $-NR^3SO_2R^4$ or $-SO_2NR^5R^6$ group.

Even more preferably, R^2 represents a phenyl, pyridyl or pyrimidinyl group, each of which may be optionally substituted by one or two substituents independently selected from a halogen atom or an amino, cyano, nitro, C_1-C_4-alkyl, halo-C_1-C_4-alkyl, C_1-C_4-alkoxy or $-SO_2NR^5R^6$ group.

Most preferably, R^2 represents a phenyl or pyridyl group optionally substituted by one or two substituents independently selected from a fluorine or chlorine atom or an amino, cyano, nitro, trifluoromethyl, methoxy or $-SO_2NR^5R^6$ group.

Preferably, R^3 and R^4 each independently represent a hydrogen atom or a C_1-C_4-alkyl group (e.g. methyl or ethyl group).

Preferably, R^5 and R^6 each independently represent a hydrogen atom or a C_1-C_4-alkyl group (e.g. methyl or ethyl group), or together with the nitrogen atom to which they are attached form a pyrrolidinyl or piperidinyl group, especially a pyrrolidinyl group.

Preferred compounds of the invention include:

(+/-)-(*N*-[1-(Biphenyl-4-yloxy)-4-(3-pyridyl)-2-butyl]-pyrrolidine-2,5-dione,

(+/-)-*N*-[1-(3'-Methoxybiphenyl-4-yloxy)-4-(3-pyridyl)-2-butyl]-pyrrolidine-2,5-dione,

(+/-)-*N*-[1-(Biphenyl-4-yloxy)-4-(3-pyridyl)-2-butyl]-thiazolidine-2,4-dione,

(+/-)-*N*-[1-(3'-Chlorobiphenyl-4-yloxy)-4-(3-pyridyl)-2-butyl]-pyrrolidine-2,5-dione,

(+/-)-*N*-[1-(3'-Fluorobiphenyl-4-yloxy)-4-(3-pyridyl)-2-butyl]-pyrrolidine-2,5-dione,

(+/-)-*N*-[1-(3'-Methoxybiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-pyrrolidine-2,5-dione,

(+/-)-*N*-[1-(3'-Methoxybiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-thiazolidine-2,4-dione,

(2*R*)-*N*-[1-(3'-Cyanobiphenyl-4-yloxy)-4-(3-pyridyl)-2-butyl]-thiazolidine-2,4-dione,

(2*R*)-*N*-[1-(3'-Nitrobiphenyl-4-yloxy)-4-(3-pyridyl)-2-butyl]-pyrrolidin-2,5-dione,

(2*R*)-*N*-[1-(3'-Cyanobiphenyl-4-yloxy)-4-(3-pyridyl)-2-butyl]-pyrrolidin-2,5-dione,

(+/-)-*N*-[1-(3'-Nitrobiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-thiazolidin-2,4-dione,

(+/-)-*N*-[1-(3'-Nitrobiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-pyrrolidin-2,5-dione,

(+/-)-*N*-[1-(4'-Fluorobiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-pyrrolidin-2,5-dione,

(+/-)-*N*-[1-(4'-Fluorobiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-thiazolidin-2,4-dione,

(+/-)-*N*-[1-(Biphenyl-4-yloxy)-4-(3-pyridyl)-2-butyl]-oxazolidine-2-one,

(2*R*)-*N*-[1-(3'-Chloro-4'-fluorobiphenyl-4-yloxy)-4-(3-pyridyl)-2-butyl]-thiazolidin-2,4-dione,

(2*R*)-*N*-[1-(3'-Chloro-4'-fluorobiphenyl-4-yloxy)-4-(3-pyridyl)-2-butyl]-pyrrolidin-2,5-dione,

(2*R*)-*N*-[1-(3',5'-Dicyanobiphenyl-4-yloxy)-4-(3-pyridyl)-2-butyl]-thiazolidin-2,4-dione,

(+/-)-*N*-[1-(3'-Nitrobiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-oxazolidin-2-one,

(2*R*)-*N*-[1-(3'-Fluorobiphenyl-4-yloxy)-4-(3-pyridyl)-2-butyl]-thiazolidin-2,4-dione,

(+/-)-*N*-[1-(3'-(Trifluoromethyl)biphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-thiazolidin-2,4-dione,

(+/-)-*N*-[1-(2'-Methoxybiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-thiazolidin-2,4-dione,

(+/-)-*N*-[1-(3'-Nitrobiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-piperidin-2,6-dione,

(+/-)-*N*-[1-(3'-Aminobiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-thiazolidin-2,4-dione,

(+/-)-*N*-[1-(3'-Nitrobiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-[1,3]-oxazinan-2-one,

(2*S*)-*N*-[1-(3'-Cyanobiphenyl-4-yloxy)-4-(3-pyridyl)-2-butyl]-thiazolidine-2,4-dione,

(2*S*)-*N*-[1-(3'-Aminobiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-thiazolidin-2,4-dione,

(2*S*)-*N*-[1-(3'-Methanesulfonamidobiphenyl-4-yloxy)-4-(3-pyridyl)-2-butyl]thiazolidine-2,4-dione,

(2*S*,3*S*)-*N*-[1-(3'-(Pyrrolidine-1-sulfonyl)biphenyl-4-yloxy)-4-(3-pyridyl)-3-pentyl]-pyrrolidine-2,5-dione,

(2*S*,3*S*)-*N*-[1-(3'-Cyano-4'-fluorobiphenyl-4-yloxy)-4-(3-pyridyl)-3-pentyl]-pyrrolidine-2,5-dione,

(2*S*)-*N*-[1-(3'-Cyano-4'-fluorobiphenyl-4-yloxy)-4-(3-pyridyl)-2-butyl]-thiazolidine-2,4-dione,

(+/-)-*N*-[1-(4'-Fluoro-3'-sulfonamidobiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-oxazolidin-2-one,

(+/-)-*N*-[1-(4-(6-Methoxypyridin-2-yl)-phenoxy)-4-(4-pyridyl)-2-butyl]-oxazolidin-2-one,

(+/-)-*N*-[1-(Biphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-oxazolidin-2-one,

(+/-)-*N*-[1-(4'-Chlorobiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-oxazolidin-2-one,

(+/-)-*N*-[1-(4'-Methylbiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-oxazolidin-2-one,

(+/-)-*N*-[1-(4'-Methoxybiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-oxazolidin-2-one,

(+/-)-*N*-[1-(3',4'-Dichlorobiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-oxazolidin-2-one,

(+/-)-*N*-[1-(4-(6-Methoxypyridin-2-yl)-phenoxy)-4-(4-pyridyl)-2-butyl]-piperidin-2,6-dione,

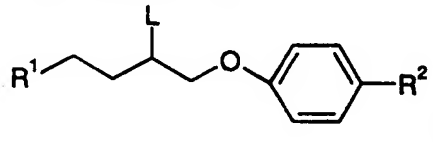
(+/-)-*N*-[1-(3'-Nitrobiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-imidazolidine-2,4-dione,

(+/-)-*N*-[1-(3'-Nitrobiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-piperidin-2-one, and

(+/-)-*N*-[1-(3'-Nitrobiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-pyrrolidin-2-one.

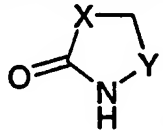
The present invention further provides a process for the preparation of a compound of formula (I) as defined above which comprises:

(a) reacting a compound of general formula



(II)

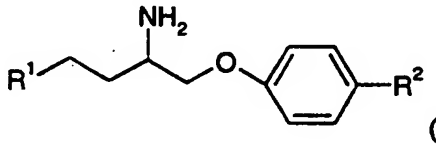
wherein L represents a leaving group (e.g. a hydroxyl group) and R^1 and R^2 are as hereinbefore defined, with a compound of general formula



(III)

wherein X and Y are as hereinbefore defined except that when X is an oxygen atom or OCH_2 group, then Y is not a CH_2 group; or

(b) when X is an oxygen atom and Y is a CH_2 group, reacting a compound of general formula



(IV)

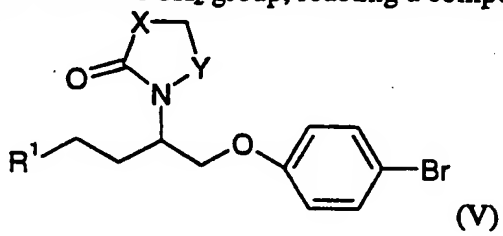
wherein R^1 and R^2 are as hereinbefore defined, with 2-chloroethyl chloroformate; or

(c) when X is an OCH_2 group and Y is a CH_2 group, reacting a compound of formula (IV) as defined in (b) above, with 3-chloropropanol in the presence of phosgene; or

(d) when X is a CH_2 group and Y is a CH_2 group, reacting a compound of formula (IV) as defined in (b) above, with 4-chlorobutyryl chloride; or

(e) when X is a CH_2CH_2 group and Y is a CH_2 group, reacting a compound of formula (IV) as defined in (b) above, with 5-valerylchloride; or

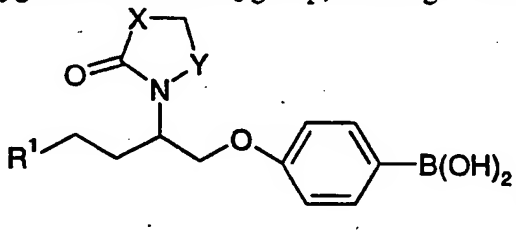
(f) when X is an oxygen atom or OCH_2 group, reacting a compound of general formula



(V)

wherein X represents an oxygen atom or OCH_2 group and Y and R^1 are as hereinbefore defined, with a compound of general formula (VI), R^2-$B(OH)_2$, wherein R^2 is as hereinbefore defined; or

(g) when X is an oxygen atom or OCH_2 group, reacting a compound of general formula



(VII)

wherein X represents an oxygen atom or OCH_2 group and Y and R^1 are as hereinbefore defined, with a compound of general formula (VIII), R^2-Br, wherein R^2 is as hereinbefore defined;

and optionally after (a), (b), (c), (d), (e), (f) or (g) converting the compound of formula (I) to a further compound of formula (I) and/or forming a pharmaceutically acceptable salt or solvate of the compound of formula (I).

The processes (a), (b), (c), (d), (e), (f) and (g) may conveniently be carried out in a solvent (e.g. dichloromethane, chloroform, acetonitrile, dioxan or tetrahydrofuran), at a temperature in the range from 0 to 100 °C, preferably in the range from 10 to 80 °C, and especially at ambient temperature (20 °C).

The compounds of formula (II) are known from WO 97/20815 and WO 98/42670 or may be prepared by processes analogous to those described in WO 97/20815 and WO 98/42670.

The compounds of formula (III), (VI) and (VIII) are known or commercially available compounds, or may be prepared by processes known in the art.

The compounds of formula (IV) may be prepared by methods known in the art starting from the compounds of formula (II).

The compounds of formula (V) and (VII) may be prepared by processes analogous to (a), (b) or (c) above using the corresponding bromo- or boron-containing compound of formula (II) or (IV).

It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups such as hydroxyl or amino groups in the intermediate compounds may need to be protected by protecting groups. Thus, the final stage in the preparation of the compounds of formula (I) may involve the removal of one or more protecting groups.

The protection and deprotection of functional groups is described in 'Protective Groups in Organic Chemistry', edited by J.W.F. McOmie, Plenum Press (1973) and 'Protective Groups in Organic Synthesis', 2nd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1991).

The compounds of formula (I) can be converted into further compounds of formula (I) using standard procedures. For example, compounds of formula (I) where R^2 is a nitrophenyl group can be converted to compounds of formula (I) where R^2 is an aminophenyl group by reduction using iron powder and ammonium chloride in ethanol or an ethanol/water mixture under reflux conditions.

The compounds of formula (I) above may be converted to a pharmaceutically-acceptable salt or solvate thereof, preferably an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulphonate or *p*-toluenesulphonate, or an alkali metal salt such as a sodium or potassium salt.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the compounds of formula (I) and mixtures thereof including racemates. Tautomers and mixtures thereof also form an aspect of the present invention.

The compounds of the present invention are advantageous in that they possess pharmacological activity. They are therefore indicated as pharmaceuticals for use in the

treatment or prevention of rheumatoid arthritis, osteoarthritis, psoriasis, allergic dermatitis, asthma, hyperresponsiveness of the airway, septic shock, glomerulonephritis, irritable bowel disease, Crohn's disease, ulcerative colitis, atherosclerosis, growth and metastases of malignant cells, myocardial ischaemia, cardiac reperfusion damage, cerebral ischaemia, stroke, myoblastic leukaemia, diabetes, Alzheimer's disease, osteoporosis, burn injury, stroke, varicose veins and meningitis.

Accordingly, the present invention provides a compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

In another aspect, the invention provides the use of a compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

The invention further provides a method of effecting immunosuppression (e.g. in the treatment of rheumatoid arthritis, irritable bowel disease, atherosclerosis or psoriasis) which comprises administering a therapeutically effective amount of a compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as hereinbefore defined to a patient.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated.

The compounds of formula (I) and pharmaceutically-acceptable salts and solvates thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) compound/salt/solvate (active ingredient) is in association with a pharmaceutically-acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.10 to 70 %w, of active ingredient, and, from 1 to 99.95 %w, more preferably from 30 to 99.90 %w, of a pharmaceutically-acceptable adjuvant, diluent or carrier, all percentages by weight being based on total composition.

Thus, the present invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as hereinbefore defined in association with a pharmaceutically-acceptable adjuvant, diluent or carrier.

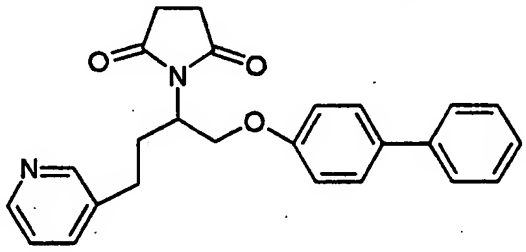
The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as hereinbefore defined with a pharmaceutically-acceptable adjuvant, diluent or carrier.

The pharmaceutical composition of the invention may be administered topically (e.g. to the lung and/or airways or to the skin) in the form of solutions, suspensions, heptafluoroalkane aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules, or by parenteral administration in the form of solutions or suspensions, or by subcutaneous administration or by rectal administration in the form of suppositories or transdermally.

The present invention will be further understood by reference to the following illustrative examples in which the terms MS, NMR and DMSO denote respectively mass spectrometry, nuclear magnetic resonance and dimethylsulphoxide.

Example 1

(+/-)-(*N*-[1-(Biphenyl-4-yloxy)-4-(3-pyridyl)-2-butyl]-pyrrolidine-2,5-dione



To a solution of triphenylphosphine (0.16 g) in tetrahydrofuran (2 ml) was added diethyl azodicarboxylate (0.1 ml); a slight exotherm was noted. The resulting orange solution was stirred for 5 minutes before addition of succinimide (0.062 g) and stirring was continued for a further 5 minutes before addition of (±)-1-(biphenyl-4-yloxy)-4-(3-pyridyl)-2-butanol (0.10 g) prepared as described in Example 25 of WO 97/20815. After stirring for

1.5 hours, the reaction mixture was concentrated under reduced pressure and the residue obtained purified by silica gel chromatography, eluting with ethyl acetate to deliver the title compound as a colourless solid (0.09 g).

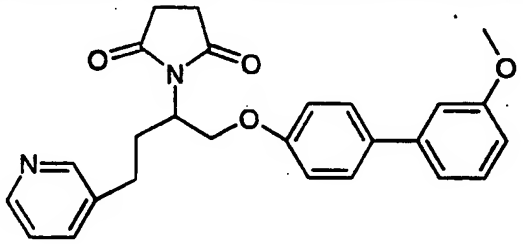
Melting point: 150-151 °C

MS (APCI +ve) 401 $(M+H)^+$

^{1}H NMR (DMSO-d_6) δ 8.42-8.40 (2H, m), 7.64 -7.55 (5H, m), 7.43 (2H, t), 7.33-7.28 (2H, m), 6.97 (2H, d), 4.45-4.33 (2H, m), 4.27-4.23 (1H, m), 2.62-2.57 (6H, m), 2.32-2.24 (1H, m), 2.11-2.02 (1H, m)

Example 2

(+/-)-*N*-[1-(3'-Methoxybiphenyl-4-yloxy)-4-(3-pyridyl)-2-butyl]-pyrrolidine-2,5-dione



Prepared according to the method of Example 1 above with succinimide (0.30 g) and (±)-1-(3'-methoxybiphenyl-4-yloxy)-4-(3-pyridyl)-2-butanol (0.25g) prepared as described in Example 42 of WO 97/20815 to give the title compound as a white solid (0.17 g).

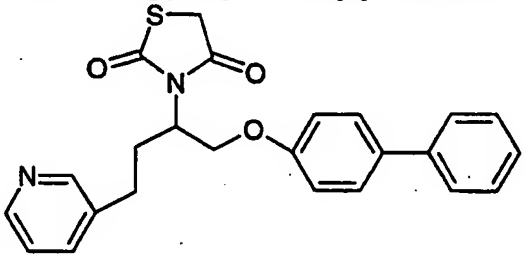
Melting point: 92-94 °C

MS (EI) 430 $(M+H)^+$

^{1}H NMR (DMSO-d_6) δ 8.42-8.40 (2H, m), 7.61 (1H, m), 7.59 (2H, t), 7.33-7.28 (2H, m), 7.16 (1H, d), 7.12 (1H, t), 6.97 (2H, d), 6.88 (1H, dd), 4.44-4.33 (2H, m), 4.26-4.24 (1H, m), 3.81 (3H, s), 2.62-2.57 (6H, m), 2.32-2.24 (1H, m), 2.11-2.02 (1H, m)

Example 3

(+/-)-*N*-[1-(Biphenyl-4-yloxy)-4-(3-pyridyl)-2-butyl]-thiazolidine-2,4-dione



Prepared according to the method of Example 1 above with (±)-1-(biphenyl-4-yloxy)-4-(3-pyridyl)-2-butanol (0.32 g) prepared as described in Example 25 of WO 97/20815 and 2,4-thiazolinedione (0.23 g) to give the title compound as a white solid (0.08 g).

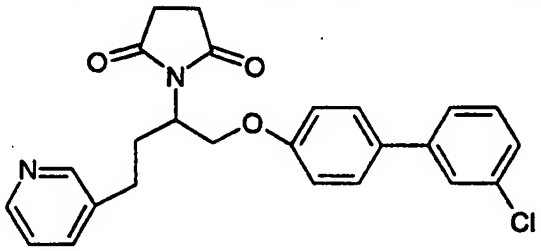
Melting point: 125-126 °C

MS (FAB) 419 $(M+H)^+$

^{1}H NMR (DMSO-d_6) δ 8.42-8.40 (2H, m), 7.55 -7.49 (5H, m), 7.41 (2H, t), 7.33-7.28 (2H, m), 6.97 (2H, d), 4.76 (1H, m), 4.52 (1H, t), 4.16 (1H, dd), 3.83 (2H, s), 2.73-2.60 (2H, m), 2.55-2.49 (1H, m), 2.15-2.06 (1H, m)

Example 4

(+/-)-*N*-[1-(3'-Chlorobiphenyl-4-yloxy)-4-(3-pyridyl)-2-butyl]-pyrrolidine-2,5-dione



Prepared according to the method of Example 1 above with (±)-1-(3'-chlorobiphenyl-4-yloxy)-4-(3-pyridyl)-2-butanol (0.42 g) prepared as described in Example 33 of WO 97/20815 and succinimide (0.24 g) to give the title compound as a white solid (0.21 g).

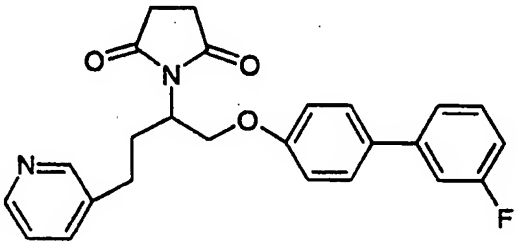
Melting point: 154 °C

MS (APCI +ve) 436/438 $(M+H)^+$

^{1}H NMR (DMSO-d_6) δ 8.47-8.45 (2H, m), 7.53 -7.23 (8H, m), 6.92 (2H, d), 4.63 (1H, m), 4.50 (1H, t), 4.16 (1H, dd), 2.73 (1H, m), 2.62-2.57 (6H, m), 2.11-2.02 (1H, m)

Example 5

(+/-)-*N*-[1-(3'-Fluorobiphenyl-4-yloxy)-4-(3-pyridyl)-2-butyl]-pyrrolidine-2,5-dione



Prepared according to the method of Example 1 above with (±)-1-(3'-fluorobiphenyl-4-yloxy)-4-(3-pyridyl)-2-butanol (0.05 g) prepared as described in Example 43 of WO 97/20815 and succinimide (0.03 g) to give the title compound as a white solid (0.06 g).

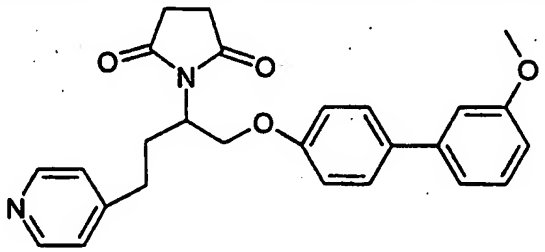
Melting point: 148 °C

MS (APCI +ve) 419 $(M+H)^+$

^{1}H NMR (DMSO-d_6) δ 8.42-8.40 (2H, m), 7.54-7.45 (3H, m), 7.38-7.20 (4H, m), 7.01 (1H, m), 6.91 (2H, d), 4.62 (1H, m), 4.50 (1H, t), 4.16 (1H, dd), 2.75-2.47 (2H, m), 2.56 (4H, s), 2.53 (1H, m), 2.11-2.02 (1H, m)

Example 6

(+/-)-*N*-[1-(3'-Methoxybiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-pyrrolidine-2,5-dione



a) (+/-)-4-Bromophenyloxymethyloxirane

To a solution of 4-bromophenol (17 g) and epichlorohydrin (25 ml) in acetonitrile (50 ml) was added caesium carbonate (24 g) and the resulting suspension was heated at reflux for 4 hours. The reaction mixture was then concentrated under reduced pressure and the residue obtained was partitioned between ether and water. An organic phase was separated, washed with brine, dried over magnesium sulphate ($MgSO_4$) and concentrated under reduced pressure to yield another residue. Distillation of the residue under vacuum gave the sub-title compound as a colourless oil (13 g).

Boiling point: 140 °C (oil pump)

MS (gcms) 228/230 M^+

b) (+/-)-1-(4-Bromophenyloxy)-4-(4-pyridyl)-2-butanol

To a solution of 4-methylpyridine (1.2 g) in tetrahydrofuran (10 ml) cooled to -78 °C was added a hexanes solution of n-butyl lithium (5.8 ml of a 2.5M solution) and the reaction mixture was warmed to 0 °C, whereupon it was added slowly via a cannula to a solution of 4-bromophenyloxymethyloxirane (3.0 g) prepared as described in step a) above in tetrahydrofuran (5 ml) cooled to 0 °C. After stirring for 1.5 hours at ambient temperature, the reaction mixture was firstly quenched by addition of aqueous ammonium chloride solution and secondly extracted with ethyl acetate. An organic phase was then separated, washed with brine, dried over magnesium sulphate ($MgSO_4$) and concentrated under reduced pressure to yield a residue. Purification of the residue by silica gel

chromatography (eluting with 5% methanol in dichloromethane) gave the sub-title compound as a yellow solid (1.8 g).

MS (APCI +ve) 322/324 $(M+H)^+$

c) **(+/-)-1-(3'-Methoxybiphenyl-4-yloxy)-4-(4-pyridyl)-2-butanol**

A mixture of 1-(4-bromophenyloxy)-4-(4-pyridyl)-2-butanol (1.8 g) prepared as described in step b) above, 3-methoxyphenylboronic acid (0.90 g), tetrakis-(triphenylphosphine)palladium(0) (0.16 g), aqueous sodium carbonate (3.5 ml of a 2M solution), ethanol (2 ml) and toluene (7.5 ml) was heated to reflux temperature for 1.5 hours. The reaction mixture was partitioned between ethyl acetate and water and an organic phase was separated, washed with brine, dried over magnesium sulphate ($MgSO_4$) and then concentrated under reduced pressure to yield a residue. Purification of the residue by silica gel chromatography (eluting with 5% methanol in dichloromethane) gave the sub-title compound as a white solid (1.0 g).

Melting point: 74-76 °C
MS (APCI +ve) 350 $(M+H)^+$

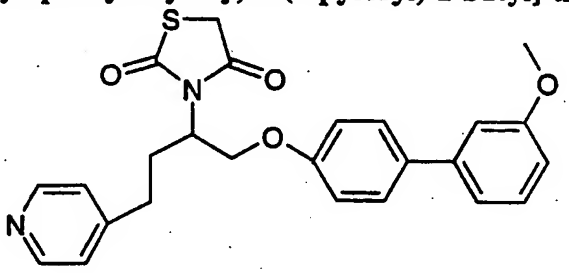
d) **(+/-)-*N*-[1-(3'-Methoxybiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-pyrrolidine-2,5-dione**

Prepared according to the method of Example 1 with (+/-)-1-(3'-methoxybiphenyl-4-yloxy)-4-(4-pyridyl)-2-butanol (0.42 g) prepared as described in step c) above and succinimide (0.30 g) to give the title compound as a white solid (0.15 g).

Melting point: 111-113 °C
MS (EI) 431 $(M+H)^+$
^1H NMR (DMSO-d_6) δ 8.42 (2H, s), 7.48 (2H, d), 7.34 (1H, t), 7.15 (3H, m), 7.06 (1H, m), 6.88 (2H, d), 6.84 (1H, m), 4.61 (1H, m), 4.47 (1H, t), 4.16 (1H, dd), 3.83 (3H, s), 2.78 (1H, m), 2.61-2.50 (2H, m), 2.46 (4H, s), 2.11-2.02 (1H, m)

Example 7

(+/-)-*N*-[1-(3'-Methoxybiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-thiazolidine-2,4-dione



Prepared according to the method of Example 1 above with (+/-)-1-(3'-methoxybiphenyl-4-yloxy)-4-(4-pyridyl)-2-butanol (0.10g) prepared as described in Example 6c) above and 2,4-thiazolinedione (0.067 g) to give the title compound as a colourless solid (0.07 g).

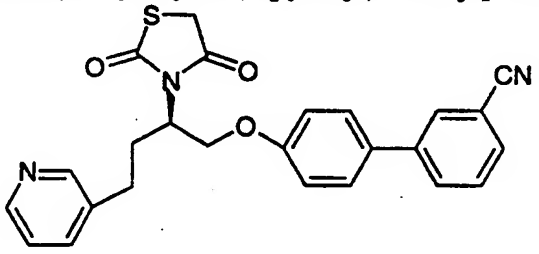
Melting point: 111-112 °C

MS (EI) 449 $(M+H)^+$

^{1}H NMR (DMSO-d_6) δ 8.46 (2H, d), 7.58 (2H, d), 7.34 (1H, t), 7.23 (2H, d), 7.17 (2H, d), 7.12 (1H, d), 6.88 (2H, d), 4.53 (1H, m), 4.44 (1H, t), 4.28 (1H, dd), 4.18 (2H, s), 3.81 (3H, s), 2.62 (2H, t), 2.37-2.24 (1H, m), 2.16-2.06 (1H, m)

Example 8

(2*R*)-*N*-[1-(3'-Cyanobiphenyl-4-yloxy)-4-(3-pyridyl)-2-butyl]-thiazolidine-2,4-dione



Prepared according to the method of Example 1 above with (2*S*)-1-(3'-cyanobiphenyl-4-yloxy)-4-(3-pyridyl)-2-butanol (0.20g) prepared as described in Example 38 of WO 97/20815 and 2,4-thiazolinedione (0.13 g) to give the title compound as a white solid (0.14 g).

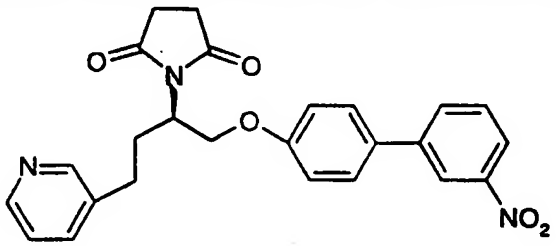
Melting point: 110-112 °C

MS (EI) 444 $(M+H)^+$

^{1}H NMR (DMSO-d_6) δ 8.43 (2H, m), 8.10 (1H, s), 7.97 (1H, d), 7.76 (1H, d), 7.70-7.60 (4H, m), 7.32 (1H, dd), 7.01 (2H, d), 4.56 (1H, m), 4.46 (1H, t), 4.30 (1H, dd), 4.19 (2H, s), 2.65 (2H, t), 2.30 (1H, m), 2.09 (1H, m)

Example 9

(2*R*)-*N*-[1-(3'-Nitrobiphenyl-4-yloxy)-4-(3-pyridyl)-2-butyl]-pyrrolidin-2,5-dione



Prepared according to the method of Example 1 above with (2*S*)-1-(3'-nitrobiphenyl-4-yloxy)-4-(3-pyridyl)-2-butanol (0.10 g) prepared as described in Example 41 of WO 97/20815 and succinimide (0.054 g) to give the title compound as a white solid (0.03 g).

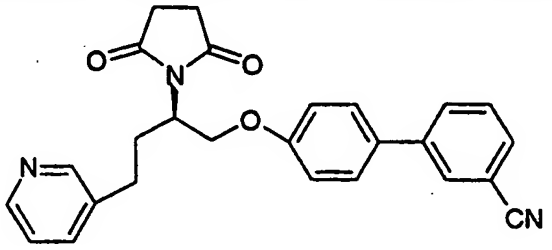
Melting point: 115-117 °C

MS (EI) 446 $(M+H)^+$

^{1}H NMR (DMSO-d_6) δ 8.40 (3H, m), 8.14 (2H, s), 7.72 (3H, m), 7.63 (1H, d), 7.32 (1H, ddd), 7.03 (2H, d), 4.42 (2H, m), 4.28 (1H, dd), 2.61 (6H, m), 2.28 (1H, m), 2.07 (1H, m)

Example 10

(2*R*)-*N*-[1-(3'-Cyanobiphenyl-4-yloxy)-4-(3-pyridyl)-2-butyl]-pyrrolidin-2,5-dione



Prepared according to the method of Example 1 above with (2*S*)-1-(3'-cyanobiphenyl-4-yloxy)-4-(3-pyridyl)-2-butanol (0.15g) prepared as described in Example 38 of WO 97/20815 and succinimide (0.09 g) to give the title compound as a white solid (0.09 g).

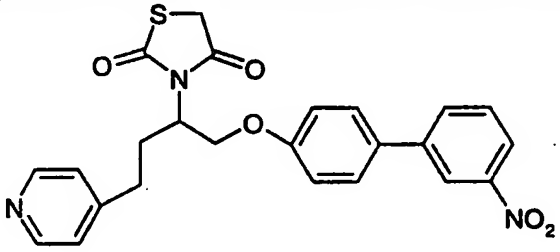
Melting point: 136-137 °C

MS (EI) 426 $(M+H)^+$

^1H NMR (DMSO-d_6) δ 8.41 (2H, m), 8.11 (1H, s), 7.97 (1H, d), 7.77 (1H, d), 7.69-7.60 (4H, m), 7.32 (1H, dd), 6.99 (2H, d), 4.39 (2H, m), 4.28 (1H, dd), 2.60 (6H, m), 2.27 (1H, m), 2.02 (1H, m)

Example 11

(+/-)-*N*-[1-(3'-Nitrobiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-thiazolidin-2,4-dione



a) **(+/-)-1-(3'-Nitrobiphenyl-4-yloxy)-4-(4-pyridyl)-2-butanol**

Prepared according to the method of Example 6c) above using 1-(4-bromophenyloxy)-4-(4-pyridyl)-2-butanol (3.12 g) as prepared in Example 6b) and 3-nitrophenylboronic acid (2.59 g), to give the sub-title compound as an orange oil (2.20 g).

MS (APCI +ve) 365 $(M+H)^+$

b) (+/-)-*N*-[1-(3'-Nitrobiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-thiazolidin-2,4-dione

Prepared according to the method of Example 1 above with (+/-)-1-(3'-nitrobiphenyl-4-yloxy)-4-(4-pyridyl)-2-butanol (0.14 g) prepared as described in step a) above and 2,4-thiazolinedione (0.09 g) to give the title compound as a pale yellow solid (0.11 g).

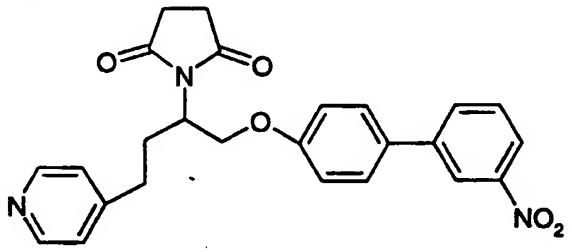
Melting point: 145-150 °C

MS (EI) 446 $(M+H)^+$

^{1}H NMR (DMSO-d_6) δ 8.47 (2H, d), 8.38 (1H, s), 8.17 (1H, d), 8.11 (1H, d), 7.75 -7.70 (3H, m), 7.23 (2H, dd), 7.04 (2H, d), 4.60-4.44 (2H, m), 4.31 (1H, dd), 4.19 (2H, s), 2.65 (2H, t), 2.32 (1H, m), 2.09 (1H, m)

Example 12

(+/-)-*N*-[1-(3'-Nitrobiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-pyrrolidin-2,5-dione



Prepared according to the method of Example 1 above with (+/-)-1-(3'-nitrobiphenyl-4-yloxy)-4-(4-pyridyl)-2-butanol (0.09 g) prepared as described in Example 11a) and succinimide (0.05 g) to give the title compound as a yellow solid (0.03 g).

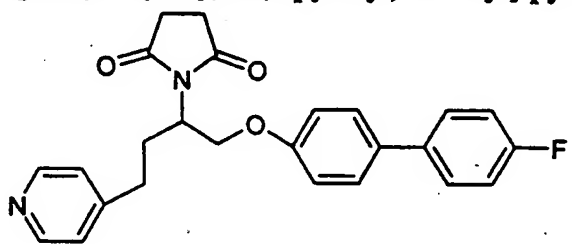
Melting point: 116-118 °C

MS (EI) 426 $(M+H)^+$

^{1}H NMR (DMSO-d_6) δ 8.46 (2H, m), 8.38 (1H, s), 8.16 (1H, d), 8.11 (1H, d), 7.75-7.70 (3H, m), 7.22 (2H, d), 7.03 (2H, d), 4.76-4.34 (2H, m), 4.28 (1H, dd), 2.65-2.60 (6H, m), 2.29 (1H, m), 2.08 (1H, m)

Example 13

(+/-)-*N*-[1-(4'-Fluorobiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-pyrrolidin-2,5-dione



a) (+/-)-1-(4'Fluorobiphenyl-4-yloxy)-4-(4-pyridyl)-2-butanol

Prepared according to the method of Example 6c) using 1-(4-bromophenyloxy)-4-(4-pyridyl)-2-butanol (0.40 g) prepared as described in Example 6b) and 4-fluorophenylboronic acid (0.28 g), to deliver the sub-title compound as a colourless solid (0.23 g).

MS (APCI +ve) 338 $(M+H)^+$

b) (+/-)-*N*-[1-(4'Fluorobiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-pyrrolidin-2,5-dione

Prepared according to the method of Example 1 above with (+/-)-1-(4'-fluorobiphenyl-4-yloxy)-4-(4-pyridyl)-2-butanol (0.10 g) prepared in step a) and succinimide (0.06 g) to give the title compound as a pale yellow solid (0.06 g).

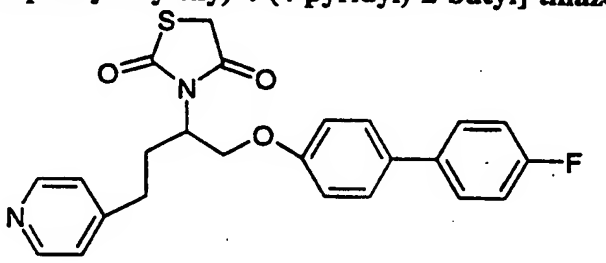
Melting point: 113-114 °C

MS (EI) 419 $(M+H)^+$

^{1}H NMR (DMSO-d_6) δ 8.46 (2H, d), 7.63 (2H, dd), 7.55 (2H, d), 7.28-7.21 (4H, m), 6.87 (2H, d), 4.45-4.33 (2H, m), 4.26 (1H, m), 2.59 (6H, m), 2.28 (1H, m), 2.08 (1H, m)

Example 14

(+/-)-*N*-[1-(4'-Fluorobiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-thiazolidin-2,4-dione



Prepared according to the method of Example 1 above with (+/-)-1-(4'-fluorobiphenyl-4-yloxy)-4-(4-pyridyl)-2-butanol (0.12g) prepared as described in Example 13a) and 2,4-thiazolinedione (0.08 g) to give the title compound as a pale grey solid (0.06 g).

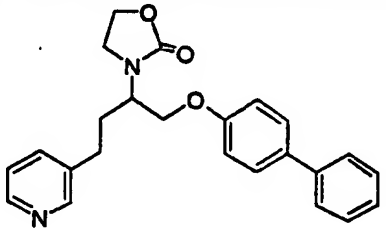
Melting point: 88-90 °C

MS (EI) 437 $(M+H)^+$

^{1}H NMR (DMSO-d_6) δ 8.46 (2H, d), 7.63 (2H, dd), 7.56 (2H, d), 7.23 (4H, m), 6.97 (2H, d), 4.50 (1H, m), 4.44 (1H, t), 4.28 (1H, dd), 4.18 (2H, s), 2.65 (2H, t), 2.30 (1H, m), 2.12 (1H, m)

Example 15

(+/-)-*N*-[1-(Biphenyl-4-yloxy)-4-(3-pyridyl)-2-butyl]-oxazolidine-2-one



a) (+/-)-*N*-[1-(Biphenyl-4-yloxy)-4-(3-pyridyl)-2-butyl]-isoindole-1,3-dione

Prepared according to the method described in Example 1 from (±)-1-(biphenyl-4-yloxy)-4-(3-pyridyl)-2-butanol (2.55g) (prepared as described in Example 25 of WO97/20815), triphenylphosphine (3.62g), diethyl azodicarboxylate (2.52ml) and phthalimide (2.36g) in tetrahydrofuran. The residue obtained purified by flash column

chromatography, eluting with hexane:ethyl acetate (3:2) gave the sub-title compound as a colourless solid (3.9g).

Melting point: 132-133 °C

MS (EI) 448 $(M+H)^+$

^{1}H NMR (DMSO-d_6) δ 8.40 (1H, d), 8.25 (1H, d), 7.85 (4H, m), 7.62-7.51 (5H, m), 7.41(2H, t), 7.29 (1H, t), 7.23(1H, dd); 6.93 (2H, d), 4.52 (2H, m), 4.38 (1H, dd), 2.70 (2H, t), 2.40 (1H, m), 2.20 (1H, m).

b) **(±)-1-(Biphenyl-4-yloxy)-4-(3-pyridyl)-2-butylamine**

(+/-)-*N*-[1-(Biphenyl-4-yloxy)-4-(3-pyridyl)-2-butyl]-isoindole-1,3-dione (3.41 g) was dissolved in a solution of 30 % methylamine in methanol (100 ml). The solution was heated to reflux temperature for 3 hours. The solvent was removed under reduced pressure, the residue dissolved in ethyl acetate, washed with water, dried over magnesium sulphate, filtered and concentrated. Purification by chromatography over neutral alumina, eluting with 10% methanol in dichloromethane gave the sub-title compound as a cream solid (1.08g).

Melting point: 52-53 °C

MS (EI) 318 $(M+H)^+$

^{1}H NMR ($CDCl_3$) δ 8.51(1H, d); 8.45(1H, d); 7.56-7.51(5H, m); 7.42(2H, t); 7.32-7.31(1H, m); 7.24-7.22(1H, m); 6.96(2H, d); 4.00-3.96(1H, m); 3.82(1H, t); 3.25-3.15(1H, m); 2.89-2.82(1H, m); 2.78-2.72(1H, m); 1.92-1.88(1H, m); 1.80-1.72(3H, m).

c) **(+/-)-*N*-[1-(Biphenyl-4-yloxy)-4-(3-pyridyl)-2-butyl]-oxazolidine-2-one**

2-Chloroethyl chloroformate (0.516ml) was added, drop-wise, to a solution of (±)-1-(biphenyl-4-yloxy)-4-(3-pyridyl)-2-butylamine (0.318g) in acetonitrile (30ml). The solution was stirred for 3 hours at ambient temperature. The solvent was removed under reduced pressure, the residue dissolved in tetrahydrofuran (5ml) and dimethylformamide

(1ml). Sodium hydride (60% dispersion in mineral oil) (0.12g) was added to the solution. Stirring continued for 1 hour at ambient temperature, water (20ml) was added to the reaction mixture, the product was extracted into ethyl acetate and organic extract dried over magnesium sulphate and concentrated under reduced pressure. Purification by silica gel chromatography eluting with 3% methanol in dichloromethane, then recrystallisation from diethylether gave the title compound as a white solid (0.093g).

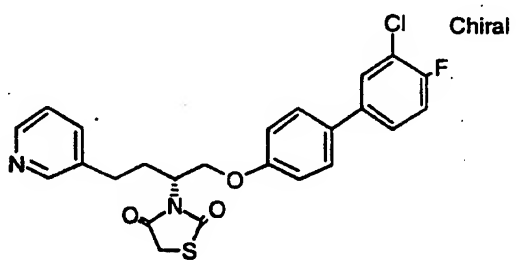
Melting point: 58-59 °C

MS (FAB) 389 $(M+H)^+$

^1H NMR ($CDCl_3$) δ 8.50-8.49(2H, m); 7.58-7.52(5H, m); 7.42(2H, t); 7.31(1H, t); 7.29-7.23(1H, m); 6.95(2H, d); 4.43-4.26(3H, m); 4.15(2H, d); 3.73-3.60(2H, m); 2.74(2H, t); 2.16-2.03(2H, m).

Example 16

(2*R*)-*N*-[1-(3'-Chloro-4'-fluorobiphenyl-4-yloxy)-4-(3-pyridyl)-2-butyl]-thiazolidin-2,4-dione



a) **(2*S*)-1-(3'-Chloro-4'-fluorobiphenyl-4-yloxy)-4-(3-pyridyl)-2-butanol**

Prepared according to the method of Example 1 with (2*R*)-1-(4-bromophenoxy)-4-(3-pyridyl)-2-butanol (0.214 g) as prepared in Example 40a) of WO 97/20815 and 3-chloro-4-fluorophenylboronic acid (0.18 g), yielding the sub-title compound as a yellow gum (0.24 g).

MS (APCI +ve) 372/374 $(M+H)^+$

b) (2*R*)-*N*-[1-(3'-Chloro-4'-fluorobiphenyl-4-yloxy)-4-(3-pyridyl)-2-butyl]-thiazolidin-2,4-dione

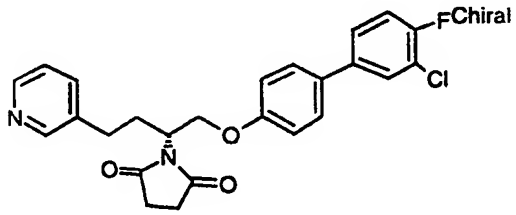
Prepared according to the method of Example 1 with (2*S*)-1-(3'-Chloro-4'-fluorobiphenyl-4-yloxy)-4-(3-pyridyl)-2-butanol (0.14g), prepared from step a) and 2,4-thiazolinedione (0.088 g) to give, after purification by silica gel chromatography (eluting with 80% ethyl acetate in iso-hexane), the title compound as a colourless gum (0.077 g).

MS (APCI +ve) 471/473 $(M+H)^+$

^{1}H NMR (DMSO-d_6) δ 8.43-8.40 (2H, m), 7.81 (1H, dd), 7.65 -7.60 (4H, m), 7.46 (1H, t), 7.32 (1H, dd), 6.97 (2H, d), 4.50 (1H, m), 4.45 (1H, t), 4.28 (1H, dd), 4.19 (2H, d), 2.64 (2H, t), 2.39-2.26 (1H, m), 2.18-2.03 (1H, m)

Example 17

(2*R*)-*N*-[1-(3'-Chloro-4'-fluorobiphenyl-4-yloxy)-4-(3-pyridyl)-2-butyl]-pyrrolidin-2,5-dione



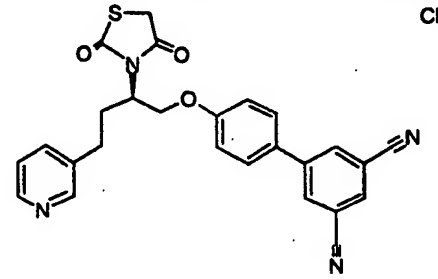
Prepared according to the method of Example 7 above with (2*S*)-1-(3'-chloro-4'-fluorobiphenyl-4-yloxy)-4-(4-pyridyl)-2-butanol (0.10g), from Example 16a) and succinimide (0.053 g) to give, after purification by silica gel chromatography (eluting with 50% acetone in iso-hexane), the title compound as a pale brown foam (0.05 g).

MS (APCI +ve) 453/455 $(M+H)^+$

^{1}H NMR (DMSO-d_6) δ 8.41 (1H, s), 8.39 (1H, m), 7.81 (1H, dd), 7.65 -7.59 (4H, m), 7.56 (1H, t), 7.32 (1H, dd), 6.97 (2H, d), 4.45-4.32 (2H, m), 4.26 (1H, m), 2.51 (6H, m), 2.25 (1H, m), 2.07 (1H, m)

Example 18

(2*R*)-*N*-[1-(3',5'-Dicyanobiphenyl-4-yloxy)-4-(3-pyridyl)-2-butyl]-thiazolidin-2,4-dione



a) **(2*S*)-1-(4-Bromophenoxy)-4-(3-pyridyl)-2-(*tert*-butyldimethylsilyloxy)butane**

A solution of (2*S*)-4-(3-pyridyl)-1,2-butanediol (10 g), prepared according to the method described in Example 26c) of WO 97/20815, and 1,1-carbonyldiimidazole (12 g) in chloroform (250 ml) was stirred at room temperature overnight. The mixture was partly concentrated under reduced pressure then filtered through a pad of silica. Evaporation of the filtrate gave a residue which was dissolved in dimethylformamide (100 ml). 4-Bromophenol (11.6 g) and caesium carbonate (16.6 g) were then added and the mixture heated at reflux temperature for 18 hours. The cooled reaction mixture was acidified with 2M hydrochloric acid and extracted with diethyl ether (x3). The aqueous phase was separated and 2M sodium hydroxide added, until the mixture achieved pH9, and extracted with ethyl acetate (x3). The combined organic extracts were dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure to give a residue. Dimethylformamide (10 ml) was added to the residue followed by imidazole (6 g) and *tert*-butyldimethylsilyl chloride (8.4 g) and the resulting mixture stirred at room temperature overnight. The reaction mixture was then added to water and extracted twice with 1:1 diethyl ether/hexane. The organic extracts were combined, dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure to give a residue. Purification by silica gel chromatography eluting with 1:1 diethyl ether/hexane delivered the sub-title compound as an oil (13.27 g).

MS (APCI +ve) 436/438 (M+H)

b) **(2*S*)-4-[4-(3-pyridyl)-2-(*tert*-butyldimethylsilyloxy)butoxy]benzeneboronic acid**

A solution of *t*-butyllithium (1.7 M in hexanes, 15.0 ml, CAUTION—PYROPHORIC) was added drop-wise to a stirred solution of (2*S*)-1-(4-bromophenoxy)-4-(3-pyridyl)-2-(*tert*-butyldimethylsilyloxy)butane (5.0 g) prepared as described in step a) above, and tri*iso*propyl borate (4.3 ml) in tetrahydrofuran (200 ml) at -78°C. After the addition was complete the reaction mixture was stirred at -70°C for 1 hour. Water (200 ml) and ethyl acetate (200 ml) were then added. The organic phase was separated, dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure to give an oil. This was purified by silica gel chromatography, eluting with 5:1 ethyl acetate/methanol to yield the sub-title compound as a foam (4.06 g).
MS (APCI +ve) 402 $(M + H)^+$

c) **(2*S*)-1-(3',5'-Dicyanobiphenyl-4-yloxy)-4-(3-pyridyl)-2-butanol**

A mixture of (2*S*)-4-[4-(3-pyridyl)-2-(*tert*-butyldimethylsilyloxy)butoxy]-benzeneboronic acid (0.479 g), prepared as described in step b), 5-bromo-1,3-benzenedicarbonitrile (0.371 g, see Ref. J. Het. Chem. (1994), 31(6), p1417-1420, Registry No. 160892-07-9), tetrakis-(triphenylphosphine)palladium(0) (0.035 g), aqueous sodium carbonate (0.9 ml of a 2M solution), toluene (10 ml), and ethanol (4ml) were heated at 100°C for 2 hours. The reaction mixture was partitioned between diethyl ether and 2N hydrochloric acid and the layers separated. The aqueous phase was neutralised with 2N sodium hydroxide and extracted with ethyl acetate. The organic phase was separated, dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure to give a residue. The residue was dissolved in tetrahydrofuran (25ml) and tetrabutylammonium fluoride (0.163 g) was added. After stirring at room temperature overnight the mixture was concentrated under reduced pressure and partitioned between diethyl ether and 2N hydrochloric acid. The layers were separated. The aqueous phase was neutralised with 2N sodium hydroxide and extracted with ethyl acetate. The organic phase was separated, dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure to give a residue. Purification by chromatography on silica gel, eluting

with 2:1 dichloromethane/acetone followed by re-crystallisation from ethyl acetate/iso-hexane gave the sub-title compound as a white solid.

MS (APCI +ve) 370 $(M+H)^+$

d) (2*R*)-*N*-[1-(3',5'-Dicyanobiphenyl-4-yloxy)-4-(3-pyridyl)-2-butyl]-thiazolidin-2,4-dione

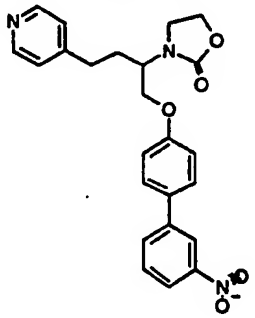
Prepared according to the method of Example 1 with (2*S*)-1-(3',5'-dicyanobiphenyl-4-yloxy)-4-(3-pyridyl)-2-butanol (0.05 g), prepared in step c) and 2,4-thiazolinedione (0.032 g) to give, after purification by super critical fluid chromatography (eluting with 0% - 45% methanol/liquid carbon dioxide), the title compound as a glass (0.015 g).

MS (APCI +ve) 469 $(M+H)^+$

^{1}H NMR (DMSO-d_6) δ 8.49 (2H, m), 8.41 (2H, m), 8.36 (1H, s), 7.80 (2H, d), 7.63 (1H, d), 7.32 (1H, dd), 7.03 (2H, m), 4.47 (2H, m), 4.31 (1H, dd), 4.19 (2H, s), 2.65 (2H, t), 2.30 (1H, m), 2.20 (1H, m)

Example 19

(+/-)-*N*-[1-(3'-Nitrobiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-oxazolidin-2-one



a) (+/-)-*N*-2-[1-(4-Bromophenoxy)-4-(4-pyridyl)-2-butyl]-isoindole-1,3-dione

Prepared according to the method of Example 15a) with 1-(4-bromophenyloxy)-4-(4-pyridyl)-2-butanol (6.02 g) prepared as described in Example 6b) and phthalimide (5.49 g) to give the sub-title compound as a golden oil (10.13 g).

MS (APCI) 451/453 $(M+H)^+$

b) **(+/-)-*N*-2-(4-Bromophenoxy)-4-(4-pyridyl)-butylamine**

Prepared according to the method of Example 15b) with (+/-)-*N*-2-[1-(4-bromophenoxy)-4-(4-pyridyl)-2-butyl]-isoindole-1,3-dione (9.78 g) to give the sub-title compound as a yellow solid (3.04 g).

Melting point: 168-169°C

MS (APCI) 321/323 $(M+H)^+$

c) **(+/-)-*N*-2-(3'-Nitrobiphenyl-4-yloxy)-4-(4-pyridyl)-butylamine**

A mixture of (+/-)-*N*-2-(4-bromophenoxy)-4-(4-pyridyl)-butylamine (0.5 g) prepared as described in step b) above, 3-nitrophenylboronic acid (0.31 g), tetrakis-(triphenylphosphine)palladium(0) (0.03 g), aqueous sodium carbonate (2M solution, 0.93 ml) and ethanol (2 ml) was heated at reflux for 4 hours. After cooling at room temperature, solvents were removed *in vacuo*. Dilute hydrochloric acid was then added and the mixture extracted with diethyl ether. The aqueous mixture was made alkaline with some solid sodium bicarbonate, and extracted with ethyl acetate. The combined extracts were dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography over neutral alumina gel eluting with dichloromethane : ethanol (98:2) then ethanol to give the sub-title compound as a yellow oil (0.28 g).

MS (APCI) 364 $(M+H)^+$

d) **(+/-)-*N*-[1-(3'-Nitrobiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-oxazolidin-2-one**

Prepared according to the method of Example 15c) with 2-chloroethyl chloroformate (0.030 ml). Final product was purified by NPHPLC eluting a gradient of 0-10% of ethanol in dichloromethane to give the title compound as a yellow foam (0.025 g).

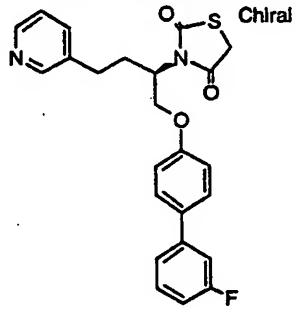
Melting point: 67-69°C

MS (APCI) 434 $(M+H)^+$

^{1}H NMR (DMSO-d_6) δ 8.46 (2H, dd), 8.39 (1H, t), 8.18-8.09 (2H,m), 7.76-7.70 (3H, m), 7.30 (2H, d), 7.09 (2H, d), 4.32-4.20(2H, m), 4.16 (2H, d), 4.14 (1H, m), 3.63-3.47 (2H, m), 2.72-2.58 (2H, m), 1.95 (2H, q)

Example 20

(2*R*)-*N*-[1-(3'-Fluorobiphenyl-4-yloxy)-4-(3-pyridyl)-2-butyl]-thiazolidin-2,4-dione



a) (2*S*)-1-(3'-Fluorobiphenyl-4-yloxy)-4-(3-pyridyl)-2-butanol

Prepared according to the method of Example 18c) above using (2*S*)-4-[4-(3-pyridyl)-2-(*tert*-butyldimethylsilyloxy)butoxy]benzeneboronic acid (0.30 g), prepared as described in Example 18b) above, and 1-bromo-3-fluorobenzene (0.15 ml), to yield the subtitled compound as a colourless oil (0.21 g).

MS (APCI +ve) 338 $(M+H)^+$

b) (2*R*)-*N*-[1-(3'-Fluorobiphenyl-4-yloxy)-4-(3-pyridyl)-2-butyl]-thiazolidin-2,4-dione

Prepared according to the method of Example 1 with (2*S*)-1-(3'Fluorobiphenyl-4-yloxy)-4-(3-pyridyl)-2-butanol (0.205g), from step a) and 2,4-thiazolinedione (0.14 g) to give, after purification by normal phase HPLC (eluting with 0% - 10% ethanol in dichloromethane) and re-crystallisation from ethanol, the title compound as a colourless solid (0.032 g).

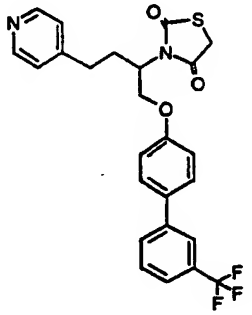
Melting point: 117-118 °C

MS (APCI +ve) 437 $(M+H)^+$

^{1}H NMR (DMSO-d_6) δ 8.42 (2H, m), 7.63 (3H, m), 7.44 (3H, m), 7.33 (1H, dd), 7.13 (1H, m), 6.98 (2H, d), 4.54 (1H, m), 4.45 (1H, t), 4.27 (1H, dd), 4.19 (2H, s), 2.62 (2H, t), 2.30 (1H, m), 2.10 (1H, m)

Example 21

(+/-)-*N*-[1-(3'-(Trifluoromethyl)biphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-thiazolidin-2,4-dione



a) **(+/-)-1-(3'-(Trifluoromethyl)biphenyl-4-yloxy)-4-(4-pyridyl)-2-butanol**

Prepared according to the method of Example 6c) using 1-(4-bromophenoxy)-4-(4-pyridyl)-2-butanol (0.20 g) prepared as described in Example 6b) and 3-trifluoromethylphenylboronic acid (0.13 g), to deliver the sub-title compound as a yellow oil (0.18 g).

MS (APCI +ve) 388 $(M+H)^+$

b) **(+/-)-*N*-[1-(3'-(Trifluoromethyl)biphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-thiazolidin-2,4-dione**

Prepared according to the method of Example 1 with (+/-)-1-(3'-trifluoromethylbiphenyl-4-yloxy)-4-(4-pyridyl)-2-butanol (0.175g), from step a) and 2,4-thiazolinedione (0.106 g). Purification of the resulting residue by silica gel chromatography (eluting with 2% methanol in dichloromethane) and super critical fluid chromatography (eluting with 0% - 45% methanol/liquid carbon dioxide) followed by

crystallisation from an ethanol/ethyl acetate/iso-hexane mixture, gave the title compound as a colourless solid (0.10g).

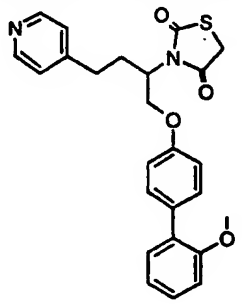
Melting point: 95-96 °C

MS (APCI +ve) 487 $(M+H)^+$

^1H NMR (DMSO-d_6) δ 8.46 (2H, m), 7.92 (2H, m), 7.67 (4H, m), 7.23 (2H, d), 7.01 (2H, m), 4.56 (1H, m), 4.46 (1H, t), 4.30 (1H, dd), 4.18 (2H, s), 2.65 (2H, t), 2.32 (1H, m), 2.10 (1H, m)

Example 22

(+/-)-*N*-[1-(2'-Methoxybiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-thiazolidin-2,4-dione



a) (+/-)-1-(2'-Methoxybiphenyl-4-yloxy)-4-(4-pyridyl)-2-butanol

Prepared according to the method of Example 6c) using 1-(4-bromophenoxy)-4-(4-pyridyl)-2-butanol (0.20 g) prepared as described in Example 6b) and 2-methoxyphenylboronic acid (0.104 g), to deliver the sub-title compound as a colourless solid (0.18g).

MS (APCI +ve) 350 $(M+H)^+$

b) (+/-)-*N*-[1-(2'-(Methoxybiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-thiazolidin-2,4-dione

Prepared according to the method of Example 1 above with (+/-)-1-(3'-methoxybiphenyl-4-yloxy)-4-(4-pyridyl)-2-butanol (0.17g), prepared in step a) above, and 2,4-thiazolinedione (0.114 g). Purification of the resulting residue by silica gel

chromatography (eluting with 2% methanol/dichloromethane) and super critical fluid chromatography (eluting with 0% - 45% methanol/liquid carbon dioxide) then crystallisation from an ethanol/ethyl acetate/iso-hexane mixture, gave the title compound as a colourless solid (0.055g).

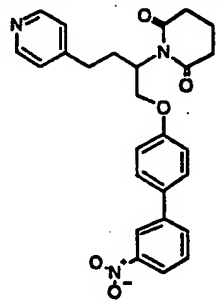
Melting point: 128-130 °C

MS (APCI +ve) 487 $(M+H)^+$

^{1}H NMR (DMSO-d_6) δ 8.46 (2H, d), 7.38 (2H, d), 7.33 - 7.22 (4H, m), 7.08 (1H, d), 6.99 (1H, m), 6.91 (2H, d), 4.55 (1H, m), 4.44 (1H, t), 4.26 (1H, dd), 4.18 (2H, s), 3.75 (3H, s), 2.65 (2H, t), 2.31 (1H, m), 2.10 (1H, m)

Example 23

(+/-)-*N*-[1-(3'-Nitrobiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-piperidin-2,6-dione



Prepared according to the method of Example 1 above with (+/-)-1-(3'-nitrobiphenyl-4-yloxy)-4-(4-pyridyl)-2-butanol (0.25 g) prepared as described in Example 11a) and glutarimide (0.16 g) to give the title compound as a pale yellow foam (0.11 g).

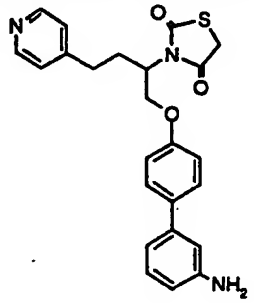
Melting point: 53-55°C

MS (APCI) 460 $(M+H)^+$

^{1}H NMR (DMSO-d_6) δ 8.45 (2H, d), 8.38(1H, s), 8.17-8.09 (2H, m), 7.75-7.70 (3H, m), 7.21 (2H, d), 7.02 (2H, d), 5.10-5.00 (1H, m), 4.43-4.29 (2H, m), 2.57 (6H, t), 2.36-2.21 (1H, m), 2.16-2.01 (1H, m), 1.74 (2H, t)

Example 24

(+/-)-*N*-[1-(3'-Aminobiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-thiazolidin-2,4-dione



A yellow suspension of (+/-)-*N*-[1-(3'-Nitrobiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-thiazolidin-2,4-dione (0.377 g) prepared as in Example 11b) above, ammonium chloride (0.17 g) and iron powder (0.18g) in a 1:1 ethanol/ water mixture was heated at reflux temperature for 1.5 hours. The cooled reaction mixture was filtered. The colourless filtrate was poured into saturated sodium bicarbonate solution and extracted with ethyl acetate. The organic phase was separated, washed with water and brine, dried over sodium sulphate (Na_2SO_4) and concentrated under reduced pressure to yield a residue that was purified by normal phase HPLC (0% - 10% ethanol/dichloromethane) followed by precipitation from an ethanol/ethyl acetate/iso-hexane mixture which yielded the title compound as a colourless solid (0.34 g).

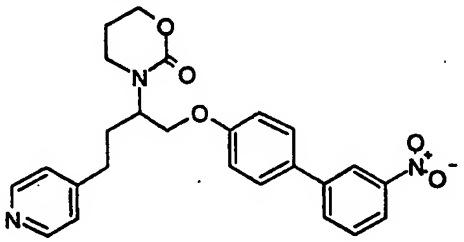
Melting point: 147-148 °C

MS (APCI +ve) 434 $(M+H)^+$

^1H NMR (DMSO-d_6) δ 8.46 (2H, d), 7.46 (2H, d), 7.23 (2H, d), 7.05 (1H, t), 6.94 (2H, d), 6.77 (1H, s), 6.71 (1H,d), 6.50 (1H, d), 5.10 (2H, s), 4.54 (1H, m), 4.43 (1H, t), 4.26 (1H, dd), 4.17 (2H, s), 2.62 (2H, t), 2.31 (1H, m), 2.12 (1H, m)

Example 25

(+/-)-*N*-[1-(3'-Nitrobiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-[1,3]-oxazinan-2-one



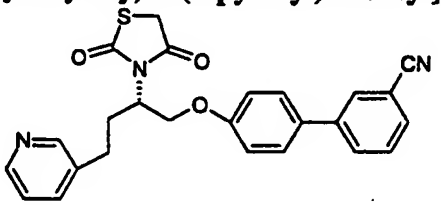
To a solution of phosgene (1.93 M in toluene, 0.31 ml) in toluene (10 ml) was added (+/-)-*N*-2-(3'-nitrobiphenyl-4-yloxy)-4-(4-pyridyl)-butylamine (0.20 g) from Step 19c) and reaction mixture stirred at room temperature for 2 hours. 3-Chloropropanol (0.09 ml) was then added to the mixture and stirred overnight at room temperature. Solvents were removed under reduced pressure and the residue was redissolved in dimethylformamide (10 ml). This solution was added slowly to a suspension of sodium hydride (60% dispersion in oil, 0.09 g) in dimethylformamide (1 ml). The mixture was heated at 70°C for 9 hours. After cooling to room temperature, solvents were removed under reduced pressure. The residue was made alkaline with aqueous sodium hydroxide (2M) and extracted with ethyl acetate. The combined extracts were dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure. The residue was purified by NPHPLC eluting a gradient of 0-10% ethanol in dichloromethane to give the title compound as a yellow oil (0.009 g).

MS (APCI) 448 $(M+H)^+$

^{1}H NMR (DMSO-d_6) δ 8.46 (2H, dd), 8.39 (1H, t), 8.18-8.09 (2H, m), 7.75-7.70 (3H, m); 7.29 (2H, dd), 7.09 (2H, dd), 4.48-4.33 (1H, m), 4.20-4.12 (4H, m), 3.31-3.21 (2H, m), 2.65 (2H, t), 2.07-1.86 (4H, m)

Example 26

(2*S*)-*N*-[1-(3'-Cyanobiphenyl-4-yloxy)-4-(3-pyridyl)-2-butyl]-thiazolidine-2,4-dione

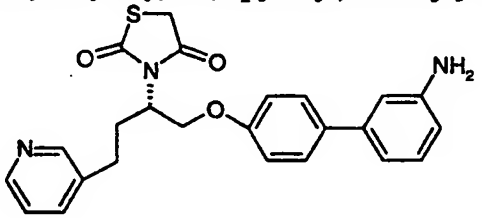


To (2*R*)-1-(3'-cyanobiphenyl-4-yloxy)-4-(3-pyridyl)-2-butanol (5μmol) prepared according to the method described in Example 37 of WO 97/20815, was added triphenylphosphine (50 μl of a 0.2M solution in tetrahydrofuran) followed by 2,4-thiazolidinedione (50 μl of a 0.2M solution in tetrahydrofuran). Diethyl azodicarboxylate (2μl) was added and the reaction mixture was capped and stirred at room temperature overnight. The mixture was concentrated under reduced pressure to give a residue. The residue was dissolved in dimethylsulphoxide to give the title compound as a 10mM solution in dimethylsulphoxide and analysed by HPLC on a 50mm x 3.9mm, 5μm particle size Waters Symmetry C8 column, eluting with 0.1% aqueous ammonium acetate solution.

MS (APCI +ve) 444 $(M+H)^+$

Example 27

(2*S*)-*N*-[1-(3'-Aminobiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-thiazolidin-2,4-dione



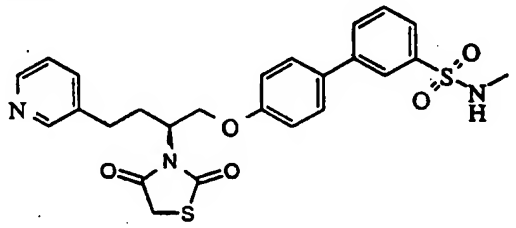
Prepared according to Example 26) above from (2*R*)-1-(3'-aminobiphenyl-4-yloxy)-4-(3-pyridyl)-2-butanol (5 μmol) prepared according to the method described in Example 50 of WO 97/20815, triphenylphosphine (50 μl of a 0.2M solution in tetrahydrofuran), 2,4-thiazolidinedione (50 μl of a 0.2M solution in tetrahydrofuran) and diethyl azodicarboxylate (2μl) to give the title compound as a 10mM solution in DMSO and

analysed by HPLC on a 50mm x 3.9mm, 5μm particle size Waters Symmetry C8 column, eluting with 0.1% aqueous ammonium acetate solution.

MS (APCI +ve) 434 $(M+H)^+$

Example 28

(2*S*)-*N*-[1-(3'-Methanesulfonamidobiphenyl-4-yloxy)-4-(3-pyridyl)-2-butyl]thiazolidine-2,4-dione

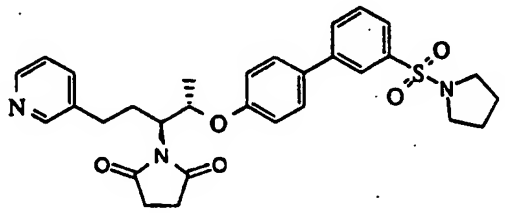


Prepared according to Example 26) above from (2*R*)-1-(3'-methanesulfonamidobiphenyl-4-yloxy)-4-(3-pyridyl)-2-butanol (5μmol) prepared according to the method described in Example 98 of WO 97/20815, triphenylphosphine (50 μl of a 0.2M solution in tetrahydrofuran), 2,4-thiazolidinedione (50 μl of a 0.2M solution in tetrahydrofuran) and diethyl azodicarboxylate (2μl) to give the title compound as a 10mM solution in DMSO and analysed by HPLC on a 50mm x 3.9mm, 5μm particle size Waters Symmetry C8 column, eluting with 0.1% aqueous ammonium acetate solution.

MS (APCI +ve) 512 $(M+H)^+$

Example 29

(2*S*,3*S*)-*N*-[1-(3'-(Pyrrolidine-1-sulfonyl)biphenyl-4-yloxy)-4-(3-pyridyl)-3-pentyl]-pyrrolidine-2,5-dione

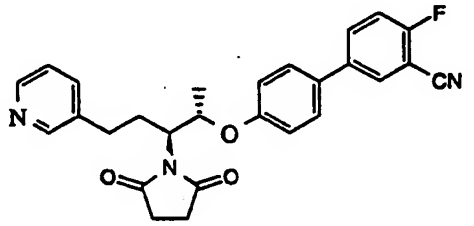


Prepared according to the method described in Example 26) using (3*R*,4*S*)-1-pyridin-3-yl-4-[3'-(pyrrolidine-1-sulfonyl)biphenyl-4-yl-oxy]pentan-3-ol (6.67μmol), prepared according to the method of Example 72 of WO 98/42670, triphenylphosphine (50 μl of a 0.27M solution in tetrahydrofuran), succinimide (50 μl of a 0.27M solution in tetrahydrofuran) and diethyl azodicarboxylate (3 μl) to give the title compound as a 10mM solution in dimethyl sulphoxide and analysed by HPLC on a 50mm x 3.9mm, 5μm particle size Waters Symmetry C8 column, eluting with 0.1% aqueous ammonium acetate solution.

MS (APCI +ve) 548 $(M+H)^+$

Example 30

(2*S*,3*S*)-*N*-[1-(3'-Cyano-4'-fluorobiphenyl-4-yloxy)-4-(3-pyridyl)-3-pentyl]-pyrrolidine-2,5-dione



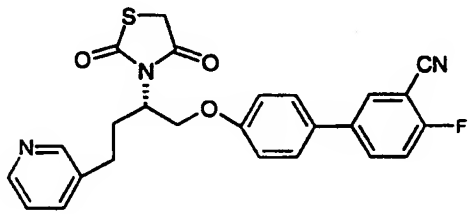
Prepared according to the method described in Example 26) using (1*S*,2*R*)-4-fluoro-4'-(2-hydroxy-1-methyl-4-pyridin-3-ylbutoxy)biphenyl-3-carbonitrile (6.67μmol), prepared according to the method of Example 36 of WO 98/42670, triphenylphosphine (50 μl of a 0.27M solution in tetrahydrofuran), succinimide (50 μl of a 0.27M solution in tetrahydrofuran) and diethyl azodicarboxylate (3 μl) to give the title compound as a 10mM

solution in DMSO and analysed by HPLC on a 50mm x 3.9mm, 5µm particle size Waters Symmetry C8 column, eluting with 5%-95% acetonitrile/ ammonium acetate.

MS (APCI +ve) 458 $(M+H)^+$

Example 31

(2*S*)-*N*-[1-(3'-Cyano-4'-fluorobiphenyl-4-yloxy)-4-(3-pyridyl)-2-butyl]-thiazolidine-2,4-dione

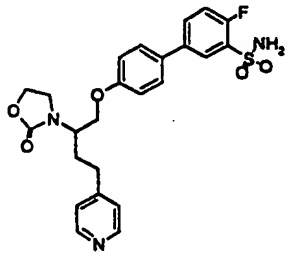


Prepared according to the method described in Example 26) using (2*R*)-1-(3'-cyano-4'-fluorobiphenyl-4-yloxy)-4-(3-pyridyl)-2-butanol (6.67µmol), triphenylphosphine (50 µl of a 0.27M solution in tetrahydrofuran), 2,4-thiazolidinedione (50 µl of a 0.27M solution in tetrahydrofuran) and diethyl azodicarboxylate (3 µl) to give the title compound as a 10mM solution in DMSO and analysed by HPLC on a 50mm x 3.9mm, 5µm particle size Waters Symmetry C8 column, eluting with 5%-95% acetonitrile/ ammonium acetate.

MS (APCI +ve) 462 $(M+H)^+$

Example 32

(+/-)-*N*-[1-(4'-Fluoro-3'-sulfonamidobiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-oxazolidin-2-one



a) (+/-)-*N*-[1-(4-Bromophenoxy)-4-(4-pyridyl)-2-butyl]- oxazolidin-2-one

Prepared according to the method described in Example 15c) using (+/-)-*N*-2-(4-bromophenoxy)-4-(4-pyridyl)-butylamine (Example 19b), 1.08 g), 2-chloroethyl chloroformate (0.521 ml) and sodium hydride (60% dispersion in mineral oil) (0.408 g). After 10 hours at 70°C, water (100 ml) was added and the product was extracted with ethyl acetate. The combined organic extracts were dried over magnesium sulphate, filtered and concentrated under reduced pressure. Residue obtained was purified by column chromatography over silica gel eluting with dichloromethane : ethanol (95: 5) to give the sub-title compound as an oil (0.651 g).

MS (APCI +ve) 391/393 $(M+H)^+$

^{1}H NMR (DMSO-d_6) δ 8.46 (2H, dd), 7.44 (2H, dd), 7.28 (2H, dd), 6.92 (2H, dd), 4.29-4.19 (2H, m), 4.07 (2H, d), 4.04-3.96 (1H, m), 3.59-3.41 (2H, m), 2.70-2.56 (2H, m), 1.90 (2H, q).

b) (+/-)-[4-(4-Pyridyl)-2-(oxazolidin-2-one-1-yl)butoxy]benzeneboronic acid

Prepared according to the method described in Example 18b) using (+/-)-*N*-[1-(4-bromophenoxy)-4-(4-pyridyl)-2-butyl]-oxazolidin-2-one (0.20 g), from step a), *tert*-butyllithium (1.7 M solution in hexanes, 0.60 ml) and tri-*iso*propylborate (0.17 ml) to give the sub-title compound as a foam (0.09 g).

MS (APCI +ve) 313 $(M-B(OH)_2)^+$

^{1}H NMR (DMSO-d_6) δ 8.56 (2H, d), 7.82 (2H, d), 7.39 (2H, d), 6.91 (2H, d), 4.25-4.15 (2H, m), 4.07 (2H, d), 4.05-3.94 (1H, m), 3.60-3.46 (2H, m), 2.74-2.62 (2H, m), 1.92 (2H, q).

c) **(+/-)-*N*-[1-(4'-Fluoro-3'-sulfonamidobiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-oxazolidin-2-one**

Prepared according to the method described in Example 6c) using (+/-)-[4-(4-Pyridyl)-2-(oxazolidin-2-one-1-yl)butoxy]benzeneboronic acid (0.090 g), from step b), 5-bromo-2-fluorophenylsulfonamide (0.097 g) (prepared in Example 35a of WO 98/42670), ethanol (1 ml), aqueous sodium bicarbonate solution (2M, 0.2 ml), tetrakis-(triphenylphosphine)palladium(0) (0.010 g).

After work-up, the residue was purified by column chromatography over silica gel eluting with dichloromethane : ethanol (95 : 5) then dichloromethane : ethanol (90 : 10) to give the title compound as a solid (0.034 g).

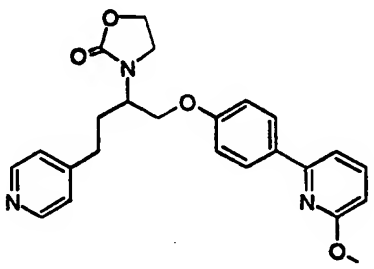
Melting point: 89-91°C

MS (APCI +ve) 486 $(M+H)^+$

^{1}H NMR (DMSO-d_6) δ 8.46 (2H, d), 7.95 (1H, dd), 7.91-7.86 (1H, m), 7.72 (2H, s), 7.60 (2H, d), 7.48 (1H, t), 7.29 (2H, d), 7.07 (2H, d), 4.29-4.19 (2H, m), 4.14 (2H, d), 4.08-4.00 (1H, m), 3.63-3.47 (2H, m), 2.72-2.60 (2H, m), 1.99-1.90 (2H,m).

Example 33

(+/-)-*N*-[1-(4-(6-Methoxypyridin-2-yl)-phenoxy)-4-(4-pyridyl)-2-butyl]-oxazolidin-2-one



Prepared according to the method described in Example 6c) using (+/-)-[4-(4-Pyridyl)-2-(oxazolidin-2-one-1-yl)butoxy]benzeneboronic acid (Example 32b, 0.100 g), 2-bromo-6-methoxypyridine (J. Org. Chem., 55, (1990), 69-73, 0.079 g), ethanol (3 ml), aqueous sodium bicarbonate solution (2M, 0.2 ml) and tetrakis-(triphenylphosphine)palladium(0) (0.010 g).

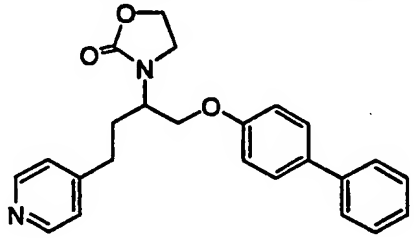
After work-up, the residue was purified by NPHPLC eluting a gradient of 0-10% ethanol in dichloromethane to give the title compound as an oil (0.082 g).

MS (APCI +ve) 420 $(M+H)^+$

^{1}H NMR (DMSO-d_6) δ 8.46 (2H, dd), 8.04 (2H, d), 7.73(1H, t), 7.48 (1H, d), 7.30 (2H, dd), 7.04 (2H, d), 6.70 (1H, d), 4.29-4.22 (2H, m), 4.15 (2H, d), 4.09-4.02 (1H, m), 3.94 (3H, s), 3.60-3.50 (2H, m), 2.73-2.59 (2H, m), 1.94 (2H, q).

Example 34

(+/-)-*N*-[1-(Biphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-oxazolidin-2-one



Prepared according to the method described in Example 6c) using (+/-)-*N*-[1-(4-bromophenoxy)-4-(4-pyridyl)-2-butyl]-oxazolidin-2-one (Example 32a), 0.100 g), phenylboronic acid (0.047 g), ethanol (3 ml), aqueous sodium bicarbonate solution (2M, 0.2 ml) and tetrakis-(triphenylphosphine)palladium(0) (0.010 g).

After work-up, the residue was purified by NPHPLC eluting a gradient of 0-10% ethanol in dichloromethane to give the title compound as a solid (0.012 g).

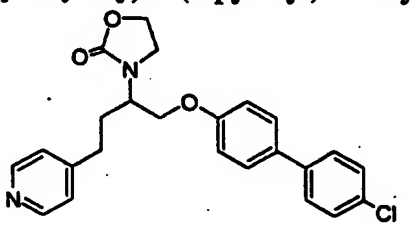
Melting point: 116-117°C

MS (APCI +ve) 389 $(M+H)^+$

^{1}H NMR (DMSO-d_6) δ 8.46 (2H, d), 7.60 (4H, t), 7.43 (2H, t), 7.30 (3H, d), 7.03 (2H, d), 4.31-4.20 (2H, m), 4.13 (2H, d), 4.07-4.00 (1H, m), 3.62-3.48 (2H, m), 2.72-2.59 (2H, m), 1.94 (2H, q)

Example 35

(+/-)-*N*-[1-(4'-Chlorobiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-oxazolidin-2-one



Prepared according to the method described in Example 6c) using (+/-)-*N*-[1-(4-bromophenoxy)-4-(4-pyridyl)-2-butyl]-oxazolidin-2-one (Example 32a), 0.100 g), 4-chlorobenzeneboronic acid (0.060 g), ethanol (3 ml), aqueous sodium bicarbonate solution (2M, 0.2 ml) and tetrakis-(triphenylphosphine)palladium(0) (0.010 g).

After work-up, the residue was purified by NPHPLC eluting a gradient of 0-10% ethanol in dichloromethane to give the title compound as a solid (0.038 g).

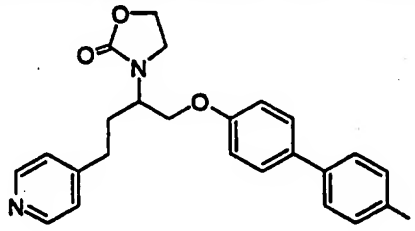
Melting point: 103-105°C

MS (APCI +ve) 423 $(M+H)^+$

^{1}H NMR (DMSO-d_6) δ 8.46 (2H, d), 7.62 (4H, q), 7.47 (2H, d), 7.29 (2H, d), 7.03 (2H, d), 4.30-4.20 (2H, m), 4.13 (2H, d), 4.07-4.00 (1H, m), 3.62-3.48 (2H, m), 2.70-2.58 (2H, m), 1.94 (2H, q).

Example 36

(+/-)-*N*-[1-(4'-Methylbiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-oxazolidin-2-one



Prepared according to the method described in Example 6c) using (+/-)-*N*-[1-(4-bromophenoxy)-4-(4-pyridyl)-2-butyl]-oxazolidin-2-one (Example 32a), 0.100 g), 4-methylbenzeneboronic acid (0.052 g), ethanol (3 ml), aqueous sodium bicarbonate solution (2M, 0.2 ml) and tetrakis-(triphenylphosphine)palladium(0) (0.010 g).

After work-up, the residue was purified by NPHPLC eluting a gradient of 0-10% ethanol in dichloromethane to give the title compound as a solid (0.033 g).

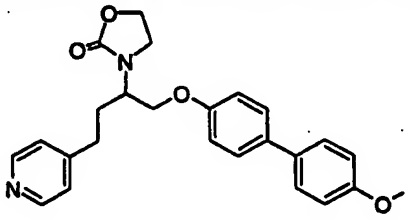
Melting point: 109-110°C

MS (APCI +ve) 403 $(M+H)^+$

^{1}H NMR (DMSO-d_6) δ 8.46 (2H, d), 7.56 (2H, d), 7.50 (2H, d), 7.29 (2H, d), 7.23 (2H, d), 7.01 (2H, d), 4.30-4.20 (2H, m), 4.12 (2H, d), 4.07-4.01 (1H, m), 3.62-3.48 (2H, m), 2.72-2.59 (2H, m), 1.94 (2H, q).

Example 37

(+/-)-*N*-[1-(4'-Methoxybiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-oxazolidin-2-one



Prepared according to the method described in Example 6c) using (+/-)-*N*-[1-(4-bromophenoxy)-4-(4-pyridyl)-2-butyl]-oxazolidin-2-one (Example 32a), 0.100 g), 4-methoxybenzeneboronic acid (0.059 g), ethanol (3 ml), aqueous sodium bicarbonate solution (2M, 0.2 ml) and tetrakis-(triphenylphosphine)palladium(0) (0.010 g).

After work-up, the residue was purified by NPHPLC eluting a gradient of 0-10% ethanol in dichloromethane to give the title compound as a solid (0.026 g).

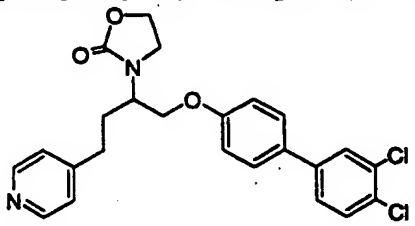
Melting point: 114-115°C

MS (APCI +ve) 419 $(M+H)^+$

^{1}H NMR (DMSO-d_6) δ 8.46 (2H, d), 7.53 (4H, dd), 7.29 (2H, d), 6.99 (4H, dd), 4.30-4.20 (2H, m), 4.11 (2H, d), 4.06-4.01 (1H, m), 3.32 (3H, s), 3.61-3.48 (2H, m), 2.70-2.59 (2H, m), 1.94 (2H, q).

Example 38

(+/-)-*N*-[1-(3',4'-Dichlorobiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-oxazolidin-2-one



Prepared according to the method described in Example 6c) using ((+/-)-[4-(4-Pyridyl)-2-(oxazolidin-2-one-1-yl)butoxy]benzeneboronic acid (Example 32b), 0.050 g), 1-bromo-3,4-dichlorobenzene (0.048 g), ethanol (2 ml), aqueous sodium bicarbonate solution (2M; 0.1 ml) and tetrakis-(triphenylphosphine)palladium(0) (0.006 g).

After work-up, the residue was purified by NPHPLC eluting a gradient of 0-10% ethanol in dichloromethane to give the title compound as a solid (0.010 g).

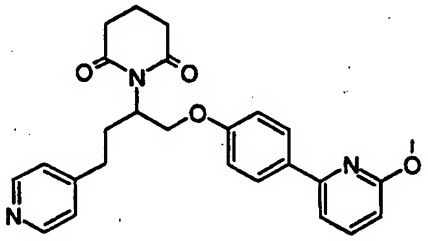
Melting point: 92-93°C

MS (APCI +ve) 457/459/461 $(M+H)^+$

^{1}H NMR (DMSO-d_6) δ 8.46 (2H, d), 7.89 (1H, d), 7.68-7.62 (4H, m), 7.29 (2H, d), 7.04 (2H, d), 4.30-4.20 (2H, m), 4.13 (2H, d), 4.07-4.01 (1H, m), 3.62-3.48 (2H, m), 2.72-2.59 (2H, m), 1.94 (2H, q).

Example 39

(+/-)-*N*-[1-(4-(6-Methoxypyridin-2-yl)-phenoxy)-4-(4-pyridyl)-2-butyl]-piperidin-2,6-dione



a) **(+/-)-1-(4-Bromophenoxy)-4-(4-pyridyl)-2-(*tert*-butyldimethylsilyloxy)butane**

tert-Butyldimethylsilyl chloride (20.53 g) and imidazole (9.25 g) were added to a solution of (+/-)-1-(4-bromophenyloxy)-4-(4-pyridyl)-2-butanol (Example 6b), 14.60 g) in dry dichloromethane (500 ml). The solution was stirred overnight at room temperature. The solid was filtered off and the filtrate concentrated under reduced pressure.

The residue was purified by chromatography over silica gel eluting with dichloromethane : ethyl acetate (5 : 1) to give the sub-title compound as a solid (19.34 g).

Melting point: 73-75°C

MS (APCI +ve) 436/438 $(M+H)^+$

^{1}H NMR (DMSO-d_6) δ 8.50 (2H, dd), 7.49 (2H, dd), 7.27 (2H, d), 6.94 (2H, dd), 4.13-4.02 (2H, m), 3.93-3.86 (1H, m), 2.82-2.68 (2H, m), 1.97-1.79 (2H, m), 0.91 (9H, s), 0.12 (3H, s), 0.09 (3H, s).

b) **(+/-)-4-[4-(4-Pyridyl)-2-(*tert*-butyldimethylsilyloxy)butoxy]benzeneboronic acid**

Prepared according to the method described in Example 18b) using (+/-)-1-(4-bromophenoxy)-4-(4-pyridyl)-2-(*tert*-butyldimethylsilyloxy)butane (10.0 g), from step a), *tert*-butyllithium (1.7 M solution in hexanes, 27 ml) and tri-*iso*propylborate (6 ml) in dry tetrahydrofuran (200 ml).

After work-up, the residue was purified by column chromatography over silica gel eluting with ethyl acetate : hexane (2 : 1) then ethyl acetate to give the sub-title compound as a foam (4.38 g).

MS (APCI +ve) 402 $(M+H)^+$

^{1}H NMR (DMSO-d_6+D_2O) δ 8.45 (2H, dd), 7.71 (2H, d), 7.24 (2H, q), 6.87 (2H, d), 4.04-3.82 (3H, m), 2.79-2.66 (2H, m), 1.97-1.75 (2H, m), 0.87 (9H, s), 0.14 (3H, s), 0.08 (3H, s).

c) **(+/-)-4-[4-(4-Pyridyl)-2-butoxy]benzeneboronic acid**

Dilute hydrochloric acid (2M, 65 ml) was added to (+/-)-1-(4-bromophenoxy)-4-(4-pyridyl)-2-(*tert*-butyldimethylsilyloxy)butane (4.38 g) from step b) in methanol (200 ml). The mixture was stirred for 2 hours at room temperature, then concentrated under reduced pressure. The residue was partitioned between diethyl ether and water. The aqueous layer was basified with aqueous sodium bicarbonate solution, then extracted with ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give the sub-title compound as a powder.

MS (APCI +ve) 288 $(M+H)^+$

^{1}H NMR (DMSO-d_6+ D_2O) δ 8.43 (2H, d), 7.71 (2H, d), 7.31 (2H, d), 6.92 (2H, d), 3.92 (2H, d), 3.84-3.78 (1H, m), 2.87-2.64 (2H, m), 1.89-1.74 (2H, m).

d) **(+/-)-1-[4-(6-Methoxypyridin-2-yl)phenoxy]-4-(4-pyridyl)-2-butanol**

Prepared according to the method described in Example 6c) using (+/-)-4-[4-(4-pyridyl)-2-butoxy]benzeneboronic acid (0.20 g) from step c), 2-bromo-6-methoxypyridine (J. Org. Chem., **55**, (1990), 69-73, 0.26 g), ethanol (3 ml), aqueous sodium bicarbonate solution (2M, 0.7 ml) and tetrakis-(triphenylphosphine)palladium(0) (0.020 g).

After work-up, the residue was purified by NPHPLC eluting a gradient of 0-10% ethanol in dichloromethane to give the sub-title compound as an oil (0.15 g).

MS (APCI +ve) 351 $(M+H)^+$

^{1}H NMR (DMSO-d_6) δ 8.45 (2H, d), 8.03 (2H, dd), 7.73 (1H, t), 7.47 (1H, d), 7.26 (2H, dd), 7.03 (2H, dd), 6.70 (1H, d), 5.08 (1H, d), 3.95 (2H, d), 3.83-3.78 (1H, m), 3.32 (3H, s), 2.85-2.77 (1H, m), 2.72-2.64 (1H, m), 1.91-1.83 (1H, m), 1.78-1.70 (1H, m)

e) **(+/-)-*N*-[1-(4-(6-Methoxypyridin-2-yl)-phenoxy)-4-(4-pyridyl)-2-butyl]-piperidin-2,6-dione**

Prepared according to the method of Example 1 using (+/-)-1-[4-(6-methoxypyridin-2-yl)phenoxy]-4-(4-pyridyl)-2-butanol (0.15 g) from step d), glutarimide (0.1 g), triphenylphosphine (0.22 g) and diethyl azodicarboxylate (0.14 ml).

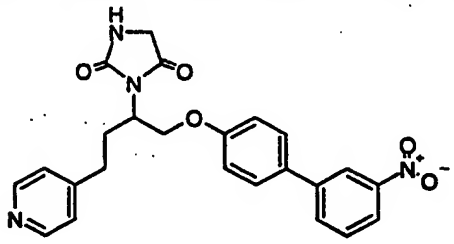
After work-up, the residue was purified by NPHPLC eluting a gradient of 0-10% ethanol in dichloromethane to give the title compound as an oil (0.10 g).

MS (APCI +ve) 446 $(M+H)^+$

^{1}H NMR (DMSO-d_6) δ 8.44 (2H, dd), 8.01 (2H, dd), 7.73 (1H, t), 7.47 (1H, d), 7.21 (2H, dd), 6.97 (2H, d), 6.70 (1H, d), 5.07-5.02 (1H, m), 4.42-4.28 (2H, m), 3.94 (3H, s), 2.62-2.51 (6H, m), 2.35-2.24 (1H, m), 2.12-2.01 (1H, m), 1.78-1.70 (2H, m).

Example 40

(+/-)-*N*-[1-(3'-Nitrobiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-imidazolidine-2,4-dione



Prepared according to the method of Example 1 using (+/-)-*N*-1-(3'-nitrobiphenyl-4-yloxy)-4-(4-pyridyl)-2-butanol (Example 15a), 0.20 g), hydantoin (0.11 g), triphenylphosphine (0.29 g) and diethyl azodicarboxylate (0.17 ml) in dry tetrahydrofuran (10 ml) and dimethylformamide (2 ml).

After work-up, the residue was purified by NPHPLC eluting a gradient of 0-10% ethanol in dichloromethane to give the title compound as a solid (0.03 g).

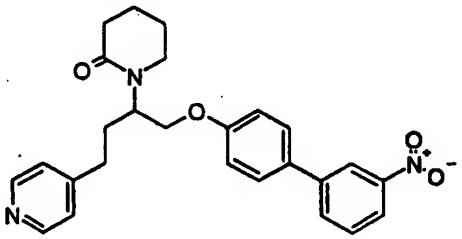
Melting point: 143-145°C

MS (APCI +ve) 447 $(M+H)^+$

^{1}H NMR (DMSO-d_6) δ 8.45 (2H, d), 8.38 (1H, s), 8.17-8.07 (3H, m), 7.74-7.70 (3H, m), 7.24 (2H, d), 7.03 (2H, d), 4.51-4.45 (1H, m), 4.38-4.23 (2H, m), 3.87 (2H, s), 2.69-2.60 (2H, m), 2.38-2.22 (1H, m), 2.16-2.00 (1H, m).

Example 41

(+/-)-*N*-[1-(3'-Nitrobiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-piperidin-2-one



5-Chlorovalerylchloride (0.07 ml) was added slowly to a solution of (+/-)-*N*-2-(3'-nitrobiphenyl-4-yloxy)-4-(4-pyridyl)-butylamine (Example 19c), 0.20 g) in dry dichloromethane (10 ml), in presence of triethylamine (1 ml). The mixture was stirred for 15 minutes at room temperature, then concentrated under reduced pressure.

Potassium *tert*-butoxide solution (1M in tetrathydrofuran, 1.5 ml) was added to the residue redissolved in anhydrous tetrahydrofuran (10 ml). After 30 minutes at room temperature, the mixture was concentrated under reduced pressure. Water was added and the mixture was extracted with ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure.

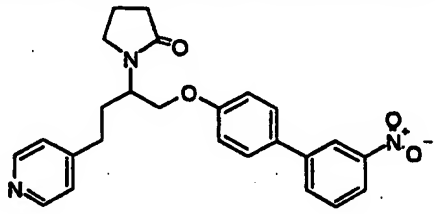
The residue was purified by NPHPLC eluting a gradient of 0-10% ethanol in dichloromethane to give the title compound as an oil (0.03 g).

MS (APCI +ve) 446 $(M+H)^+$

^{1}H NMR (DMSO-d_6) δ 8.45 (2H, d), 8.38 (1H, t), 8.18-8.09 (2H, m), 7.75-7.69 (3H, m), 7.26 (2H, d), 7.07 (2H, d), 4.86-4.76 (1H, m), 4.19-4.07 (2H, m), 3.25-3.14 (2H, m), 2.73 (2H, t), 2.28-2.22 (2H, m), 2.00-1.87 (2H, m), 1.64 (4H, bd).

Example 42

(+/-)-*N*-[1-(3'-Nitrobiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-pyrrolidin-2-one



Prepared according to the method of Example 41 above with (+/-)-*N*-2-(3'-nitrobiphenyl-4-yloxy)-4-(4-pyridyl)-butylamine (Example 19c), 0.20 g), triethylamine (1 ml), 4-chlorobutyrylchloride (0.06 ml) and potassium *tert*-butoxide solution (1M in tetrathydrofuran, 1.5 ml).

After work-up, the residue was purified by NPHPLC eluting a gradient of 0-10% ethanol in dichloromethane to give the title compound as an oil (0.035 g).

MS (APCI +ve) 432 $(M+H)^+$

^{1}H NMR (DMSO-d_6) δ 8.45 (2H, dd), 8.38 (1H, t), 8.18-8.09 (2H, m), 7.75-7.69 (3H, m), 7.28 (2H, dd), 7.07 (2H, dd), 4.34-4.27 (1H, m), 4.11 (2H, d), 3.38-3.26 (2H, m), 2.61-2.55 (2H, m), 2.24 (2H, t), 1.97-1.85 (4H, m).

Example 43

Pharmacological Analysis

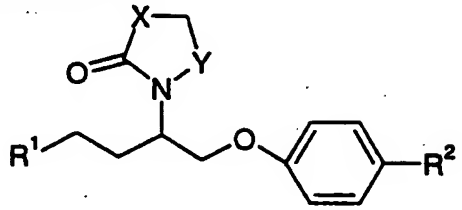
Certain compounds such as benzoylbenzoyl adenosine triphosphate (bbATP) are known to be agonists of the $P2X_7$ receptor, effecting the formation of pores in the plasma membrane (Drug Development Research (1996), 37(3), p.126). Consequently, when the receptor is activated using bbATP in the presence of ethidium bromide (a fluorescent DNA probe), an increase in the fluorescence of intracellular DNA-bound ethidium bromide is observed. The increase in fluorescence can be used as a measure of $P2X_7$ receptor activation and therefore to quantify the effect of a compound on the $P2X_7$ receptor.

In this manner, each of the title compounds of Examples 1 to 42 were tested for antagonist activity at the $P2X_7$ receptor. Thus, the test was performed in 96-well flat bottomed microtitre plates, the wells being filled with 250 µl of test solution comprising

200 µl of a suspension of THP-1 cells (2.5 x 10^6 cells/ml) containing 10^{-4}M ethidium bromide, 25 µl of a high potassium buffer solution containing 10^{-5}M bbATP, and 25 µl of the high potassium buffer solution containing 3 x 10^{-5}M test compound. The plate was covered with a plastics sheet and incubated at 37 °C for one hour. The plate was then read in a Perkin-Elmer fluorescent plate reader, excitation 520 nm, emission 595 nm, slit widths: Ex 15 nm, Em 20 nm. For the purposes of comparison, bbATP (a $P2X_7$ receptor agonist) and pyridoxal 5-phosphate (a $P2X_7$ receptor antagonist) were used separately in the test as controls. From the readings obtained, a pIC_{50} figure was calculated for each test compound, this figure being the negative logarithm of the concentration of test compound necessary to reduce the bbATP agonist activity by 50%. Each of the compounds of Examples 1 to 42 demonstrated antagonist activity, having a pIC_{50} figure > 4.50.

CLAIMS

1. A compound of general formula



(I)

wherein X represents an oxygen or sulphur atom or a group NH, CH_2, CH_2CH_2 or OCH_2;
Y represents a group CH_2 or C=O;
R^1 represents a pyridyl or pyrimidinyl group;
R^2 represents a phenyl, pyridyl or pyrimidinyl group, each of which may be optionally substituted by one or more substituents independently selected from a halogen atom or an amino, cyano, hydroxyl, nitro, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkylthio, (di)C_1-C_6-alkylamino, C_1-C_6-alkylcarbonyl, C_1-C_6-alkoxycarbonyl, C_1-C_6-alkylsulphinyl, C_1-C_6-alkylsulphonyl, $-NR^3SO_2R^4$ or $-SO_2NR^5R^6$ group, or a group $-Z-(CH_2)_p-Z-(CH_2)_q-H$ wherein each Z independently represents a nitrogen or oxygen atom, p is an integer from 2 to 5 and q is 0 or an integer from 1 to 5;
R^3 and R^4 each independently represent a hydrogen atom or a C_1-C_6-alkyl group; and
R^5 and R^6 each independently represent a hydrogen atom or a C_1-C_6-alkyl group, or together with the nitrogen atom to which they are attached form a pyrrolidinyl or piperidinyl group; or a pharmaceutically acceptable salt or solvate thereof.

2. A compound according to claim 1, wherein X represents a sulphur atom or a group CH_2.

3. A compound according to claim 1 or claim 2, wherein Y represents a group C=O.

4. A compound according to any one of claims 1 to 3, wherein R^1 represents a pyridyl group.

5. A compound according to any one of claims 1 to 4, wherein R^2 represents a phenyl, pyridyl or pyrimidinyl group, each of which may be optionally substituted by one, two or three substituents independently selected from a halogen atom or an amino, cyano, hydroxyl, nitro, C_1-C_4-alkyl, halo-C_1-C_4-alkyl, C_1-C_4-alkoxy, C_1-C_4-alkylthio, (di)C_1-C_4-alkylamino, C_1-C_4-alkylcarbonyl, C_1-C_4-alkoxycarbonyl, C_1-C_4-alkylsulphinyl, C_1-C_4-alkylsulphonyl, $-NR^3SO_2R^4$ or $-SO_2NR^5R^6$ group.

6. A compound according to any one of claims 1 to 5, wherein R^2 represents a phenyl, pyridyl or pyrimidinyl group, each of which may be optionally substituted by one or two substituents independently selected from a halogen atom or an amino, cyano, nitro, C_1-C_4-alkyl, halo-C_1-C_4-alkyl, C_1-C_4-alkoxy or $-SO_2NR^5R^6$ group.

7. A compound according to claim 1 being:

(+/-)-(*N*-[1-(Biphenyl-4-yloxy)-4-(3-pyridyl)-2-butyl]-pyrrolidine-2,5-dione,

(+/-)-*N*-[1-(3'-Methoxybiphenyl-4-yloxy)-4-(3-pyridyl)-2-butyl]-pyrrolidine-2,5-dione,

(+/-)-*N*-[1-(Biphenyl-4-yloxy)-4-(3-pyridyl)-2-butyl]-thiazolidine-2,4-dione,

(+/-)-*N*-[1-(3'-Chlorobiphenyl-4-yloxy)-4-(3-pyridyl)-2-butyl]-pyrrolidine-2,5-dione,

(+/-)-*N*-[1-(3'-Fluorobiphenyl-4-yloxy)-4-(3-pyridyl)-2-butyl]-pyrrolidine-2,5-dione,

(+/-)-*N*-[1-(3'-Methoxybiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-pyrrolidine-2,5-dione,

(+/-)-*N*-[1-(3'-Methoxybiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-thiazolidine-2,4-dione,

(2*R*)-*N*-[1-(3'-Cyanobiphenyl-4-yloxy)-4-(3-pyridyl)-2-butyl]-thiazolidine-2,4-dione,

(2*R*)-*N*-[1-(3'-Nitrobiphenyl-4-yloxy)-4-(3-pyridyl)-2-butyl]-pyrrolidin-2,5-dione,

(2*R*)-*N*-[1-(3'-Cyanobiphenyl-4-yloxy)-4-(3-pyridyl)-2-butyl]-pyrrolidin-2,5-dione,

(+/-)-*N*-[1-(3'-Nitrobiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-thiazolidin-2,4-dione,

(+/-)-*N*-[1-(3'-Nitrobiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-pyrrolidin-2,5-dione,

(+/-)-*N*-[1-(4'-Fluorobiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-pyrrolidin-2,5-dione,

(+/-)-*N*-[1-(4'-Fluorobiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-thiazolidin-2,4-dione,

(+/-)-*N*-[1-(Biphenyl-4-yloxy)-4-(3-pyridyl)-2-butyl]-oxazolidine-2-one,

(2*R*)-*N*-[1-(3'-Chloro-4'-fluorobiphenyl-4-yloxy)-4-(3-pyridyl)-2-butyl]-thiazolidin-2,4-dione,

(2*R*)-*N*-[1-(3'-Chloro-4'-fluorobiphenyl-4-yloxy)-4-(3-pyridyl)-2-butyl]-pyrrolidin-2,5-dione,

(2*R*)-*N*-[1-(3',5'-Dicyanobiphenyl-4-yloxy)-4-(3-pyridyl)-2-butyl]-thiazolidin-2,4-dione,

(+/-)-*N*-[1-(3'-Nitrobiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-oxazolidin-2-one,

(2*R*)-*N*-[1-(3'-Fluorobiphenyl-4-yloxy)-4-(3-pyridyl)-2-butyl]-thiazolidin-2,4-dione,

(+/-)-*N*-[1-(3'-(Trifluoromethyl)biphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-thiazolidin-2,4-dione,

(+/-)-*N*-[1-(2'-Methoxybiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-thiazolidin-2,4-dione,

(+/-)-*N*-[1-(3'-Nitrobiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-piperidin-2,6-dione,

(+/-)-*N*-[1-(3'-Aminobiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-thiazolidin-2,4-dione,

(+/-)-*N*-[1-(3'-Nitrobiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-[1,3]-oxazinan-2-one,

(2*S*)-*N*-[1-(3'-Cyanobiphenyl-4-yloxy)-4-(3-pyridyl)-2-butyl]-thiazolidine-2,4-dione,

(2*S*)-*N*-[1-(3'-Aminobiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-thiazolidin-2,4-dione,

(2*S*)-*N*-[1-(3'-Methanesulfonamidobiphenyl-4-yloxy)-4-(3-pyridyl)-2-butyl]thiazolidine-2,4-dione,

(2*S*,3*S*)-*N*-[1-(3'-(Pyrrolidine-1-sulfonyl)biphenyl-4-yloxy)-4-(3-pyridyl)-3-pentyl]-pyrrolidine-2,5-dione,

(2*S*,3*S*)-*N*-[1-(3'-Cyano-4'-fluorobiphenyl-4-yloxy)-4-(3-pyridyl)-3-pentyl]-pyrrolidine-2,5-dione,

(2*S*)-*N*-[1-(3'-Cyano-4'-fluorobiphenyl-4-yloxy)-4-(3-pyridyl)-2-butyl]-thiazolidine-2,4-dione,

(+/-)-*N*-[1-(4'-Fluoro-3'-sulfonamidobiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-oxazolidin-2-one,

(+/-)-*N*-[1-(4-(6-Methoxypyridin-2-yl)-phenoxy)-4-(4-pyridyl)-2-butyl]-oxazolidin-2-one,

(+/-)-*N*-[1-(Biphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-oxazolidin-2-one,

(+/-)-*N*-[1-(4'-Chlorobiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-oxazolidin-2-one,

(+/-)-*N*-[1-(4'-Methylbiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-oxazolidin-2-one,

(+/-)-*N*-[1-(4'-Methoxybiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-oxazolidin-2-one,

(+/-)-*N*-[1-(3',4'-Dichlorobiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-oxazolidin-2-one,

(+/-)-*N*-[1-(4-(6-Methoxypyridin-2-yl)-phenoxy)-4-(4-pyridyl)-2-butyl]-piperidin-2,6-dione,

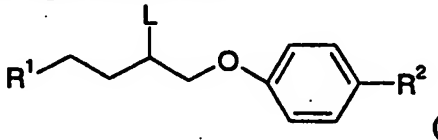
(+/-)-*N*-[1-(3'-Nitrobiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-imidazolidine-2,4-dione,

(+/-)-*N*-[1-(3'-Nitrobiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-piperidin-2-one, or

(+/-)-*N*-[1-(3'-Nitrobiphenyl-4-yloxy)-4-(4-pyridyl)-2-butyl]-pyrrolidin-2-one.

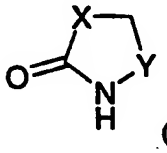
8. A process for preparing a compound of formula (I) as defined in claim 1 which comprises

(a) reacting a compound of general formula



(II)

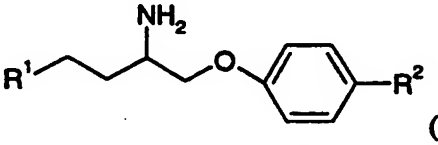
wherein L represents a leaving group and R^1 and R^2 are as defined in formula (I), with a compound of general formula



(III)

wherein X and Y are as defined in formula (I) except that when X is an oxygen atom or OCH_2 group, then Y is not a CH_2 group; or

(b) when X is an oxygen atom and Y is a CH_2 group, reacting a compound of general formula



(IV)

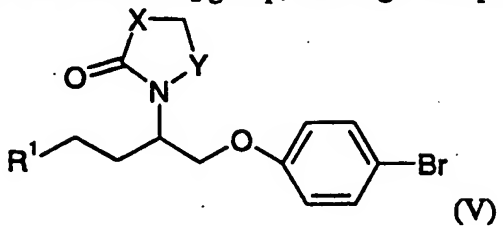
wherein R^1 and R^2 are as defined in formula (I), with 2-chloroethyl chloroformate; or

(c) when X is an OCH_2 group and Y is a CH_2 group, reacting a compound of formula (IV) as defined in (b) above, with 3-chloropropanol in the presence of phosgene; or

(d) when X is a CH_2 group and Y is a CH_2 group, reacting a compound of formula (IV) as defined in (b) above, with 4-chlorobutyryl chloride; or

(e) when X is a CH_2CH_2 group and Y is a CH_2 group, reacting a compound of formula (IV) as defined in (b) above, with 5-valerylchloride; or

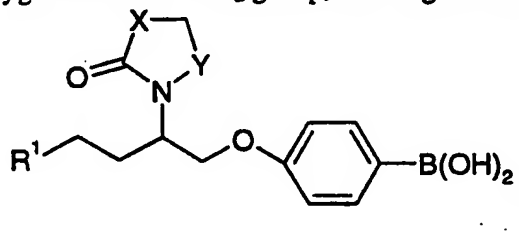
(f) when X is an oxygen atom or OCH_2 group, reacting a compound of general formula



(V)

wherein X represents an oxygen atom or OCH_2 group and Y and R^1 are as defined in formula (I), with a compound of general formula (VI), R^2-$B(OH)_2$, wherein R^2 is as defined in formula (I); or

(g) when X is an oxygen atom or OCH_2 group, reacting a compound of general formula



(VII)

wherein X represents an oxygen atom or OCH_2 group and Y and R^1 are as defined in formula (I), with a compound of general formula (VIII), R^2-Br, wherein R^2 is as defined in formula (I);

and optionally after (a), (b), (c), (d), (e), (f) or (g) converting the compound of formula (I) to a further compound of formula (I) and/or forming a pharmaceutically acceptable salt or solvate of the compound of formula (I).

9. A pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as claimed in any one of claims 1 to 7 in association with a pharmaceutically-acceptable adjuvant, diluent or carrier.

10. A process for the preparation of a pharmaceutical composition as claimed in claim 9 which comprises mixing a compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as defined in any one of claims 1 to 7 with a pharmaceutically-acceptable adjuvant, diluent or carrier.

11. A compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as claimed in any one of claims 1 to 7 for use in therapy.

12. Use of a compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as claimed in any one of claims 1 to 7 in the manufacture of a medicament for use in therapy.

13. A method of effecting immunosuppression which comprises administering to a patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as claimed in any one of claims 1 to 7.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 98/02190

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 405/06, C07D 413/06, C07D 417/06, C07D 401/06, A61K 31/44
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" erlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 March 1999	19 -03- 1999
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Göran Karlsson Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 98/02190

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 13
because they relate to subject matter not required to be searched by this Authority, namely:

A method for treatment of the human or animal body by therapy, see rule 39.1.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.